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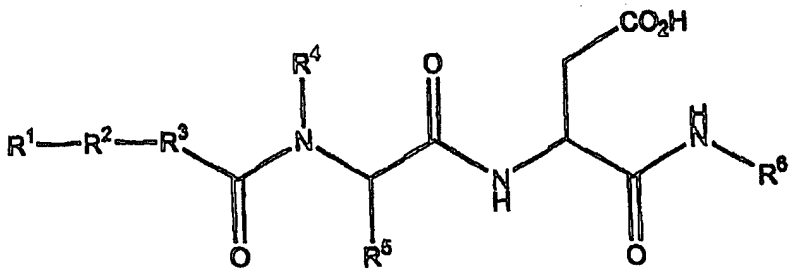

(1)

(57) Abstract

The present invention is directed to compounds of formula (1) and pharmaceutically-acceptable derivatives thereof.

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NOVEL COMPOUNDS

This application is a continuation-in-part of application Serial No. 08/821,825, filed March 21, 1997, which was converted to provisional application No. _____ (yet to be assigned), the entire contents of which are incorporated herein by reference.

Technical Field

The present invention relates to novel compounds that inhibit VLA-4 binding.

Background

Cell movement through an organism is critical for many normal and pathological processes. The movement of leukocytes, ameboid cells in blood, is particularly important for the function of immune processes.

Cell movement is controlled by specific receptors on the surface of cells. The VLA-4 receptor, also known as the $\alpha 4\beta 1$ or CD49d/CD29 receptor, is expressed on the surface of some cells and is known to control the movement of those cells. The VLA-4 receptor is expressed on and controls the movement of leukocytes including, for example, mature T and B lymphocytes, natural killer cells, monocytes, basophils and eosinophils. See, for example, Hemler, *Ann. Rev. Immunol.*, 8:365-400 (1990), and Hemler *et al.*, *Immunol. Rev.*, 114:45-65 (1990).

The VLA-4 receptor controls cell movement by binding to specific counter receptors. Specific counter receptors include, for example, the cytokine-inducible vascular cell adhesion molecule-1 (VCAM-1) and the extracellular matrix protein

fibronectin. See, for example, Elices *et al.*, *Cell*, 60:577-584 (1990) and Wayner *et al.*, *J. Cell Biol.*, 109:1321-1330 (1989).

The VCAM-1 counter receptor is expressed on a variety of cells. For example, the VCAM-1 is expressed on the surface of endothelial cells, which line the vascular system. The expression of VCAM-1 on those cells is induced by pro-inflammatory cytokines such as, IL-1, TNFα, and IL-4, and is an early event in the development of inflammation. See, for example, Osborn *et al.*, *Cell*, 59:1203-1211 (1989). The amino acid sequence within VCAM-1 that binds to the VLA-4 receptor has the amino acid sequence Gln-Ile-Asp-Ser-Pro. See, for example, Clements *et al.*, *J. Cell Sci.*, 107:2127-2135 (1992); and Osborn *et al.*, *J. Cell Biol.*, 124:601-608 (1994).

The amino acid sequence within the fibronectin counter receptor that binds the VLA-4 receptor also has been identified. See, for example, Wayner *et al.*, *J. Cell. Biol.*, 109:1321-1330 (1989). That sequence comprises a 25-amino acid sequence, termed CS-1, and the minimal amino acid sequence within CS-1 that binds to the VLA-4 receptor has the amino acid sequence Leu-Asp-Val. See, for example, Humphries *et al.*, *J. Cell Biol.*, 103:2637-2647 (1986); Wayner WO 91/03252, published March 21, 1991; Wayner WO 93/12809, published July 8, 1993; and Humphries, WO 92/13887, published August 20, 1992.

The VLA-4 receptor is particularly important in the control of leukocyte movement into inflamed tissue. The VLA-4 receptor guides the leukocytes to inflamed tissue by binding to counter receptors expressed as a result of inflammation, such as VCAM-1 on endothelial cells induced by pro-

inflammatory cytokines. That binding causes the circulating leukocytes to stop circulating and attach to the vascular wall at the site of inflammation. The attached leukocytes can then migrate into adjacent inflamed tissues.

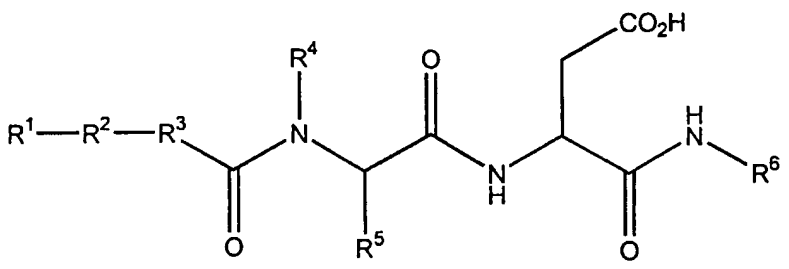
Evidence for VLA-4 receptor's control of leukocyte movement during inflammation is provided by *in vivo* studies. Specifically, antibodies and small molecule antagonists to VLA-4 receptors that block the receptor's interaction with counter receptors have been shown to inhibit inflammatory reactions *in vivo*. Inflammation in specific organs, such as the skin, brain, kidney, lung and gut have been shown to be VLA-4 receptor dependent, mostly as a result of recruiting lymphocytes, monocytes and eosinophils. See, for example, Elices, M.J., "Cell Adhesion and Human Disease," published by John Wiley & Sons, London, pp. 79-90, (1995); Lobb *et al.*, *J. Clin. Invest.* 94:1722-1728 (1994).

The recruitment of leukocytes in inflamed tissue causes further inflammation to occur. Inhibiting that movement is known to reduce the resulting inflammation. Therefore, preventing the VLA-4 receptor from guiding leukocytes to inflamed tissue would be useful for treating or preventing inflammation. Inhibiting the binding of VLA-4 receptors to counter receptors would prevent the recruitment of leukocytes because the leukocytes would not attach to endothelial cells and migrate into adjacent inflamed tissue. Novel compounds thus are needed that inhibit VLA-4 binding to counter receptors for the control of leukocyte movement and the treatment of inflammation.

Brief Summary of the Invention

The present invention is directed to compounds that inhibit VLA-4 binding.

In particular, the invention is directed to the compounds of the following Formula (1):



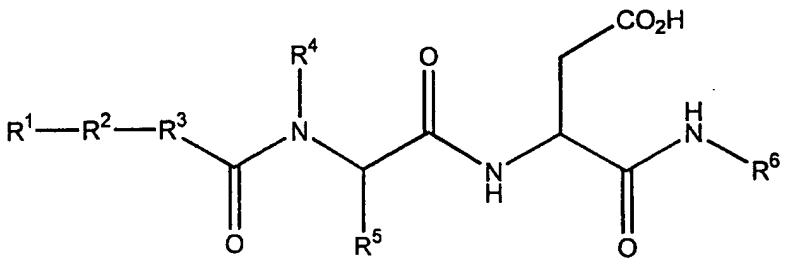
(1)

as set forth below.

The invention is also directed to a pharmaceutically-acceptable derivative of a compound of Formula 1 as described below. The invention is further directed to a pharmaceutical composition containing the compound of Formula 1 or a pharmaceutically-acceptable derivative thereof and a pharmaceutically-accepable carrier, also as described below.

Detailed Description of the Invention

The invention is directed to the compounds of the following Formula (1):

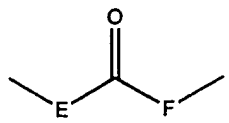


(1)

In the above Formula 1, R^1 is an alkyl group, an adamantyl group, or a 5-, 6-, 6,5-, or 6,6-membered non-heterocyclic, heterocyclic, aromatic, partially saturated or fully saturated ring that is optionally substituted by one or more nitro, fluoro, chloro, bromo, amino, lower alkylamino, di(lower alkyl)amino, hydroxy, lower alkyl, lower alkoxy, alkylcarbonyloxy, alkylcarbonylamino, alkylcarbonyl, or lower alkoxycarbonyl groups. When R^1 is such a ring, the ring is connected to R^2 either directly by a bond or indirectly through a lower alkyl group.

In the above Formula 1, R^2 is a lower alkyl, a C_2 to C_4 alkenyl, or a C_2 to C_4 alkynyl group, in which each group optionally can contain a carbonyl, ether, thioether, aminocarbonyl, sulfonamido,

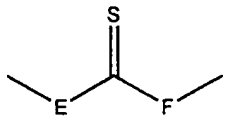
sulfone, or sulfoxide group. Alternatively, R^2 can be a group of the Formula (2) or (3):



(2)

;

or of the Formula (3):



(3)

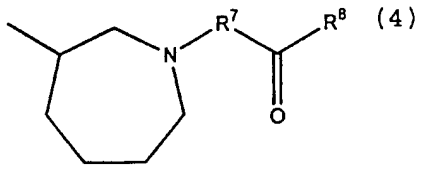
In Formulas 2 and 3, E is a CX^1X^2 group, a NX^3 group or an oxygen atom and F is a CX^4X^5 group, a NX^6 group or an oxygen atom, but E and F both are not simultaneously oxygen atoms. X^1, X^2, X^3, X^4, X^5, and X^6 are independently selected from the group consisting of a hydrogen atom or a lower alkyl group. However, if R^1 is the alkyl group, R^2 must be a group of the Formula (2) or (3).

In Formula 1, R^3 is a 5-, 6-, 6,5-, or 6,6-membered aromatic ring optionally containing from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen or sulfur atoms and is connected to the carbonyl carbon of the amide bond containing R^4 of Formula 1 either directly by a bond or indirectly through a lower alkyl group.

R^4 in the above Formula 1 is a hydrogen atom or a lower alkyl group.

R^5 in the above Formula 1 is hydrogen, a lower alkyl, or a lower alkyl amido group optionally substituted by lower hydroxyalkyl, di(lower alkyl)sulfide, or lower thioalkyl group, or a 5- or 6-membered non-heterocyclic saturated ring that is connected to the methinyl carbon of Formula 1 either directly by a bond or indirectly through a lower alkyl group.

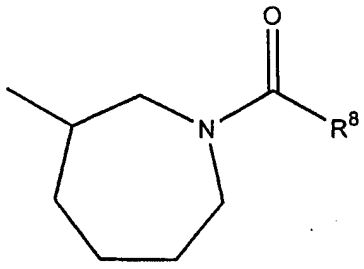
Also in Formula 1, R^6 is a group of the Formula (4):



(4)

;

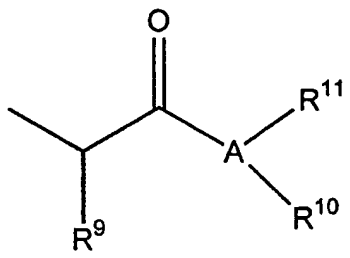
or Formula (5):



(5)

In Formula 4, R^7 is a lower alkyl group. In Formula 4 and 5, R^8 is a lower alkyl, an amino, a loweralkylamino, or a di(loweralkyl)amino group.

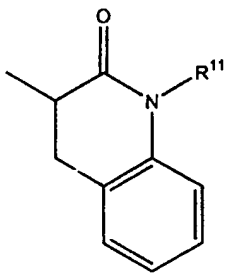
Alternatively, R^6 is a group of the Formula (6):



(6)

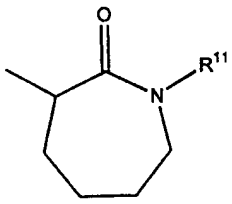
In Formula 6, A is a nitrogen or oxygen atom. When A is a nitrogen atom, R^9 is a hydrogen atom or a lower alkyl, lower hydroxyalkyl, lower thioalkyl, di(lower alkyl) sulfide group; a 6-membered non-heterocyclic aromatic, partially saturated or saturated ring or a 5-or 6-membered heterocyclic aromatic ring containing from 1 to 3 nitrogen, oxygen, or sulfur atoms, or a 3-indolyl ring. Each of these rings is connected to the methinyl carbon of Formula 6 either directly by a bond or indirectly through a lower alkyl group. The non-heterocyclic or heterocyclic aromatic ring at R^9 can optionally be substituted by a hydroxy, nitro, primary carboxamide, lower alkyl primary carboxamide, or (lower alkoxy)lower alkyl group. Alternatively, R^9

can be taken together with R^{10} to form a 6,6-membered ring of the Formula (7):



(7)

or a group of the Formula (8):



(8)

Also, when A is a nitrogen atom in Formula 6, R^{10} can be a lower alkyl, a lower hydroxyalkyl, or a N-morpholino group. Alternatively, R^{10} can be taken together with R^9 as described above, or taken together with R^{11} to form a 5- or 6-membered heterocyclic ring containing 1 or 2 nitrogen atoms and optionally containing an oxygen atom, a sulfur atom, a sulfone group or a sulfoxide group wherein the heterocyclic

ring is aromatic, partially saturated or fully saturated. The 5- or 6-membered heterocyclic ring optionally can be substituted by one or more hydroxy, lower alkyl, lower hydroxyalkyl, lower alkoxy, lower hydroxyalkoxy lower alkyl, (lower alkoxy)lower alkyl, carboxylic acid, lower alkyl carboxylic acid, primary carboxamide, lower alkyl primary carboxamide, lower alkylcarbonyloxy, phenyl, phenyl lower alkylsulfonyl, or phenylsulfonyl groups in which the phenyl group of the phenyl lower alkyl sulfonyl or phenyl sulfonyl group is optionally substituted by a lower alkyl moiety.

Finally when A is a nitrogen atom in Formula 6, R^{11} is a lower alkyl optionally substituted by one or more (lower alkyl) amino, or di (lower alkyl) amino, lower alkyl primary carboxamide, lower alkyl substituted by a morpholino group, a cyclohexyl group, a hydrogen atom or is taken together with R^{10} as described above.

When A is an oxygen atom in Formula 6, R^9 is as above except that the R^9 cannot be taken with R^{10}. R^{10} is a lower alkyl or a 6-membered non-heterocyclic or heterocyclic ring that is aromatic, partially saturated, or saturated and is connected directly to the methinyl carbon of Formula 6 by a bond or indirectly through a lower alkyl group. R^{11} is absent.

A compound of Formula 1 includes a pharmaceutically acceptable salt of the compound of Formula 1. All chiral carbon centers of a Formula 1 compound can be in in a pure R form, pure S form, or a mixture of R and S forms in any proportion. A compound of Formula 1 also includes a bioisostere of the compound of Formula 1.

A "lower alkyl" refers to a C_1 to C_4 alkyl and denotes the methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl or isobutyl groups.

An "alkyl" group is a saturated straight- or branched-carbon chain of from 1 to about 20 carbons and includes, for example, those groups exemplifying the terms "lower alkyl" and through to groups such as dodecanyl, pentadecanyl, heptadecanyl, 7-ethyloctadencanyl, 4-methyl-13-ethylheptadecanyl, eicosanyl, and the like.

By "C_2 to C_4 alkenyl" group is meant a straight- or branched-carbon chain having at least one double bond and denotes radicals such as, vinyl (-CH=CH-), allyl, crotyl, but-3-en-1-yl, dimethyl vinyl, as well as dienes of straight- and branched-carbon chains and the like.

A "C_2 to C_4 alkynyl" group is a straight- or branched-carbon chain having at least one triple bond and denotes radicals such as, ethylynyl (-C≡C-), propargyl, but-3-yn-1-yl, 2-but-2-yn-yl, as well as diynes of straight and branched chains, and the like.

A "(lower alkyl)amino" group is a lower alkyl radical bonded to an amino radical and denotes radicals such as methylamino (CH_3NH-), t-butylamino, and the like.

A "di(lower alkyl)amino" group means two lower alkyl radicals bonded to an amino radical. The lower alkyl groups can be the same or different. The term denotes groups such as dimethylamino ($(CH_3)_2N$-), (t-butyl)n-propylamine, and the like.

By "lower alkyl primary carboxamide," a group is meant as being a primary amide bonded to a lower alkyl radical which lower alkyl radical is in turn bonded to Formula 1 and denotes radicals such as methylcarboxyamide ($-CH_2CONH_2$), n-butyl carboxyamide and the like.

A "lower hydroxyalkyl" group is a hydroxyl radical bonded to a lower alkyl radical and denotes radicals such as hydroxymethyl ($-CH_2OH$) , 3-hydroxy-n-butyl, and the like.

A "lower alkyl carboxylic acid" is a carboxy radical bonded via its carbon atom to a lower alkyl radical as described above which lower alkyl radical in turn is bonded to Formula 1. The term denotes radicals such as methylcarboxylic acid ($-CH_2COOH$), n-butylcarboxylic acid and the like.

A "lower alkoxy" group is a lower alkyl radical defined above bonded to an oxygen atom radical and denotes radicals such as methoxy (CH_3O-), isopropyloxy, n-butyloxy, and the like.

A "(lower alkoxy)lower alkyl" group is an ether wherein the lower alkyl groups bound to both sides of the oxygen are the same or different and one of the lower alkyl groups is bound to the group so substituted. The term denotes radicals such as isopropyloxymethyl ($(CH_3)_2CHOCH_2-$), 2-(n-butyloxy)ethyl, and the like.

A "lower alkoxycarbonyl" group is a lower alkyl radical bonded to an ester oxygen which is bonded to a carbonyl radical. The term denotes radicals such as methoxycarbonyl ($CH_3OC(O)-$), ethoxycarbonyl and the like.

The term "lower hydroxyalkoxy lower alkyl" denotes a hydroxy radical bonded to a lower alkyl radical which is bonded to an ethereal oxygen atom bound in turn to a lower alkyl radical and denotes radicals such as hydroxymethoxymethyl ($CH_2(OH)OCH_2$-) , 1(hydroxy)n-propyloxyethyl, 4-(hydroxymethoxy)n-butyl, and the like.

A "alkylcarbonyl" group is an alkyl group bonded to a carbonyl radical and denotes radicals such as acetyl (CH_3CO-), n-eicosanoyl, and the like.

A "lower alkylcarbonyloxy" group is a lower alkyl radical bonded to the carbonyl carbon of an ester group bound through an ethereal oxygen atom and denotes radicals such as methylcarbonyloxy (CH_3COO-), n-butylcarbonyloxy, and the like.

A "lower alkyl amido" group is a lower alkyl radical bonded to the carbonyl carbon of the amide radical and denotes radicals such as methyl amido (CH_3CONH-), n-hexylamido, and the like.

A "di(lower alkyl)sulfide" group is a thioether wherein the lower alkyl groups bound on both sides of the sulfide are the same or different and one of the lower alkyl groups is bound to the group so substituted. The term denotes radicals such as methylthiomethyl (CH_3SCH_2-), methylthiobutyl, and the like.

A "lower thioalkyl" group is a lower alkyl radical bonded to a mercaptan group and denotes radicals such as methylthiol (-CH_2SH), n-butylthiol, and the like.

By the phrase "5-, 6-, 6,5-, 6,6- membered non-heterocyclic ring aromatic, partially saturated or fully saturated" is meant a monocyclic or fused bicyclic ring such as cyclopentyl, cyclohexyl, cyclohex-1,4-dienyl, phenyl, indenyl, naphthalenyl, and the like.

The term "5- or 6-membered non-heterocyclic saturated ring" denotes the radicals cyclopentanyl and cyclohexyl.

By "6-membered non-heterocyclic aromatic, partially saturated or saturated ring" is meant radicals such as cyclohexyl, cyclohex-1-enyl, phenyl, and the like.

Similarly, the phrase "a 5-, 6-, 6,5-, 6,6-membered heterocyclic ring aromatic, partially saturated or fully saturated" denotes a monocyclic- or fused bicyclic ring optionally containing 1 to 3 nitrogen, oxygen, or sulfur atoms. Examples of such rings include pyrrolyl, 3-pyrrolinyl, pyrrolidinyl, furyl, thienyl, pyridinyl, piperidinyl, pyrazinyl, piperazinyl, morpholinyl, indolyl, benzofuranyl, benzisoxazolyl, quinazolinyl, quinazolinyl, and the like.

The phrase "5-or 6-membered heterocyclic aromatic ring containing from 1 to 3 nitrogen, oxygen, or sulfur atoms" is exemplified by pyridinyl, pyridazinyl, pyrimidinyl, and pyrrolyl, imidazolyl, pyrazolyl, s-triazinyl rings, and the like.

The phrase "5-, 6-membered heterocyclic ring containing 1 or 2 nitrogen atoms and optionally containing an oxygen atom, a sulfur atom, a sulfone group or a sulfoxide group wherein the heterocyclic

ring is aromatic, partially saturated, or fully saturated and denotes radicals such as pyrazolyl, pyrrolinyl, pyrrolidinyl, furyl, thiophenyl, thioxolyl, pyridinyl, pyridazinyl, piperidinyl, pyrimidinyl, dioxanyl, morpholinyl 1,3 thiaoxaolidinyl S-oxide or S-dioxide, 1,3 thiaoxaoinyl S-oxide or S-dioxide, 1,3 thiaoxaoperhydryl S-oxide or S-dioxide, and the like.

Also, in Formula 1 the phrase "a 5-, 6-, 6,5-, or 6,6-membered aromatic ring optionally containing from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen or sulfur" denotes a ring such as pyrazolyl, phenyl, pyridazinyl, indolyl, isoquinolinyl, and the like.

The term "pharmaceutically-acceptable salt" encompasses those salts that form with the carboxylate anions and includes salts formed with the organic and inorganic cations such as those chosen from the alkali and alkaline earth metals, (for example, lithium, sodium, potassium, magnesium, barium and calcium); ammonium; and the organic cations (for example, dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzylammonium, dibenzylethylenediammonium, and like cations). Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, and the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine, and arginine, and acetic acid-like counter-ions such as acetate and trifluoroacetate. Furthermore, any zwitterionic form of the instant compounds formed by a carboxylic acid and an amino group is referred to by this term. A preferred cation for the carboxylate anion is the sodium cation. Furthermore, the term includes salts that form by standard acid-base reactions with basic

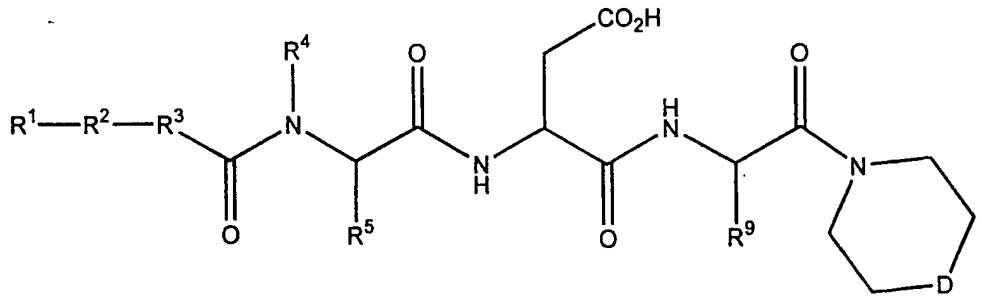
groups (such as amino groups) and organic or inorganic acids. Such acids include hydrochloric, sulfuric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, D-camphoric, glutaric, phthalic, tartaric, lauric, stearic, salicyclic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and the like acids.

The compounds of Formula 1 above and Formula 29 below may also exist as solvates and hydrates. Thus, these compounds may crystallize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of the mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

The term "bioisostere" refers to a compound differing from a compound of the invention by one or more atoms expected to produce an equivalent biological effect. An example of a bioisostereic substitution is the interchange of nitrogen and carbon in an aromatic ring. See, for example, "Medicinal Chemistry," Alfred Burger, Ed., Interscience Publishers, N.Y., 1960, pp 78-80, which is incorporated herein by reference.

One group of compounds within that of Formula 1 has the following Formula (9):

(9)



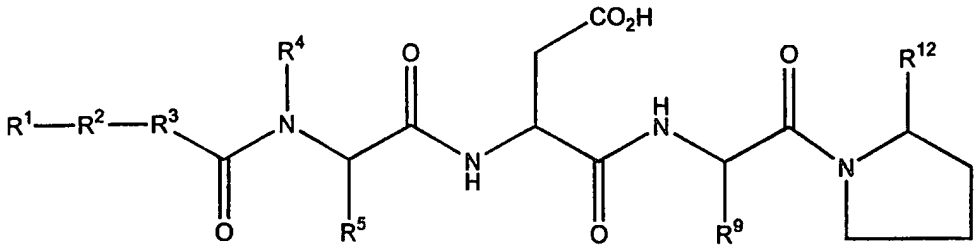
In the above Formula 9, D is an oxygen or sulfur atom or a sulfone, sulfoxide, CH_2, or NH group and the CH_2 or NH group can be optionally substituted by a lower alkyl, primary carboxamide, lower alkyl primary carboxamide, hydroxy, lower hydroxyalkyl, lower alkoxy, (lower alkoxy)lower alkyl, lower hydroxyalkoxy lower alkyl, alkylcarbonyl, carboxylic acid, lower alkyl carboxylic acid, phenyl, phenyl lower alkyl sulfonyl, phenylsulfonyl in which the phenyl of the phenyl lower alkyl sulfonyl or phenylsulfonyl is optionally substituted by a lower alkyl, or a lower alkylcarbonyloxy group.

In Formula 9, R^9 is a hydrogen atom or a lower alkyl, lower hydroxyalkyl, lower thioalkyl, di (lower alkyl) sulfide; a 5-or 6-membered non-heterocyclic aromatic, partially saturated or saturated ring or a 6-membered heterocyclic aromatic ring containing from 1 to 3 nitrogen, oxygen or sulfur atoms, or a 3-indolyl ring. Each of these rings is connected to the methinyl carbon of Formula 9 either directly by a bond or indirectly through a lower alkyl group. The non-heterocyclic or heterocyclic aromatic ring at R^9 can optionally be substituted by a hydroxy, nitro, primary carboxamide, lower alkyl primary carboxamide, or (lower alkoxy)lower alkyl group.

R^1, R^2, R^3, R^4, and R^5 in Formula 9 are as in Formula 1 above.

Another group of compounds within that of Formula 1 has the following Formula (10):

(10)



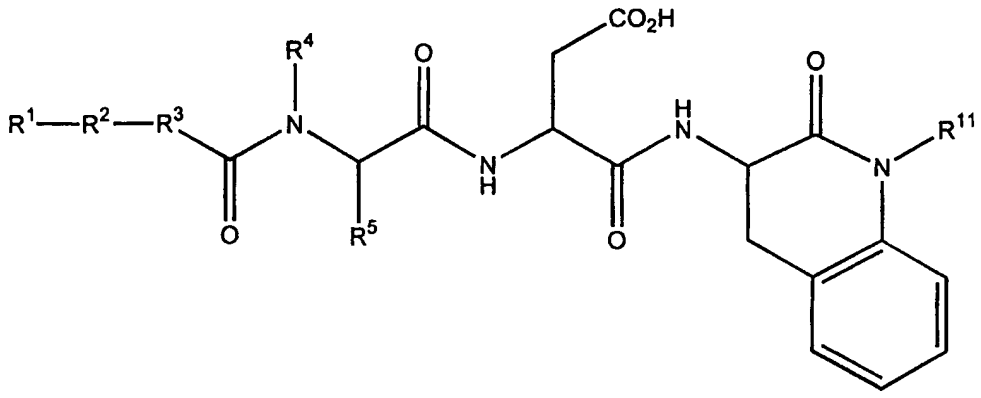
In Formula 10, R^9 is a hydrogen atom or a lower alkyl, lower hydroxyalkyl, lower thioalkyl, di (lower alkyl) sulfide; a 6-membered non-heterocyclic aromatic, partially saturated or saturated ring or a 5- or 6-membered heterocyclic aromatic ring containing from 1 to 3 nitrogen, oxygen or sulfur atoms, or a 3-indolyl ring. Each of these rings is connected to the methinyl carbon of Formula 10 either directly by a bond or indirectly through a lower alkyl group. The non-heterocyclic or heterocyclic aromatic ring at R^9 can optionally be substituted by a hydroxy, nitro, primary carboxamide, lower alkyl primary carboxamide, or (lower alkoxy) lower alkyl group.

In Formula 10, R^{12} is a hydrogen atom, carboxylic acid, a lower alkyl carboxylic acid, a primary carboxamide, a lower alkyl primary carboxamide, a lower alkyl group or a lower hydroxyalkyl.

R^1, R^2, R^3, R^4, and R^5 in Formula 10 are as in Formula 1 above.

Yet another group of compounds within that of Formula 1 has the following Formula (11):

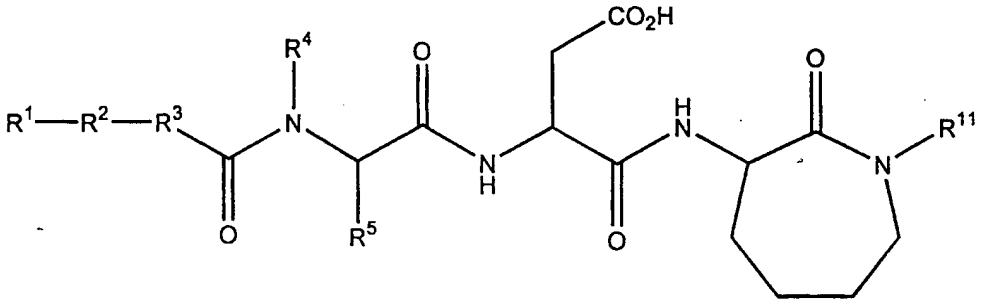
(11)



In Formula 11, R^1, R^2, R^3, R^4, R^5 and R^{11} are as in Formula 1 above.

Further still, a group of compounds of note within that of Formula 1 has the following Formula (12):

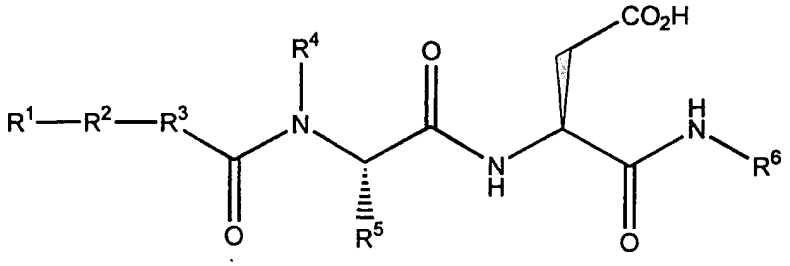
(12)



In Formula 12, R^1, R^2, R^3, R^4, R^5 and R^{11} are as in Formula 1 above.

A group of optimum compounds within that of Formula 1 has the following Formula (13):

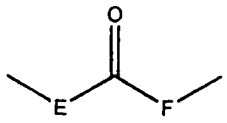
(13)



Optimum compounds of Formula 1 also occur when:

R^1 is a 5-, 6-, 6,5-, or 6,6-membered non-heterocyclic or heterocyclic, aromatic, partially saturated or fully saturated ring that is optionally substituted by one or more nitro, fluoro, chloro, bromo, amino, lower alkylamino, di(lower alkyl)amino, hydroxy, lower alkyl, lower alkoxy, alkylcarbonyloxy, alkylcarbonylamino, alkylcarbonyl, or lower alkoxycarbonyl groups and the ring is connected to R^2 either directly by a bond or indirectly through a lower alkyl group; and

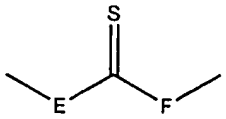
R^2 is a group of the Formula (2):



(2)

;

or of the Formula (3):



(3)

In Formulas 2 and 3, E is a CX^1X^2 group, a NX^3 group or an oxygen atom and F is a CX^4X^5 group, a NX^6 group or an oxygen atom, but E and F both are not simultaneously oxygen atoms and X^1, X^2, X^3, X^4, X^5, and X^6 are independently selected from the group consisting of a hydrogen atom or a lower alkyl group.

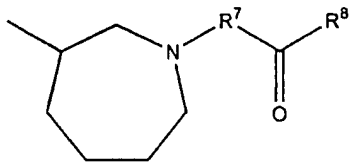
In optimum compounds, R^3 is a 6-membered aromatic ring optionally containing from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen or sulfur atoms and is connected to the carbonyl carbon of the amide bond containing R^4 of Formula 1 either directly by a bond or indirectly through a lower alkyl group.

Furthermore, optimum compounds contain a R^5 that is a lower alkyl group or a 6-membered non-heterocyclic saturated ring that is connected to the methinyl carbon of Formula 1 either directly by a bond or indirectly through a lower alkyl group.

In optimum compounds,

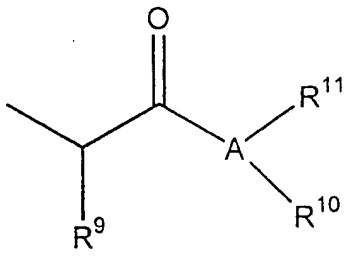
R^6 is a group of the Formula (4)

(4)



or R^6 is a group of the Formula (6)

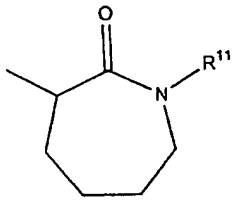
(6)



and

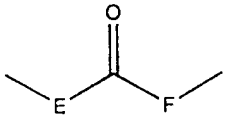
R^9 is taken together with R^{10} to form a group of the Formula (8):

(8)



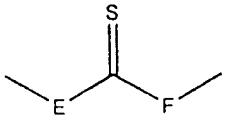
In the above optimum compounds, R^2 is a group of the Formula (2):

(2)



or of the Formula (3):

(3)



and E is a CX^1X^2 group, a NX^3 group or an oxygen atom and F is a CX^4X^5 group, a NX^6 group or an oxygen atom; and X^1, X^2, X^3, X^4, X^5, and X^6 are independently selected from the group consisting of a hydrogen atom or a lower alkyl group with the provisios that E and F both are not simultaneously oxygen atoms; and if R^1 is the alkyl group, R^2 must be a group of the Formula (2) or (3).

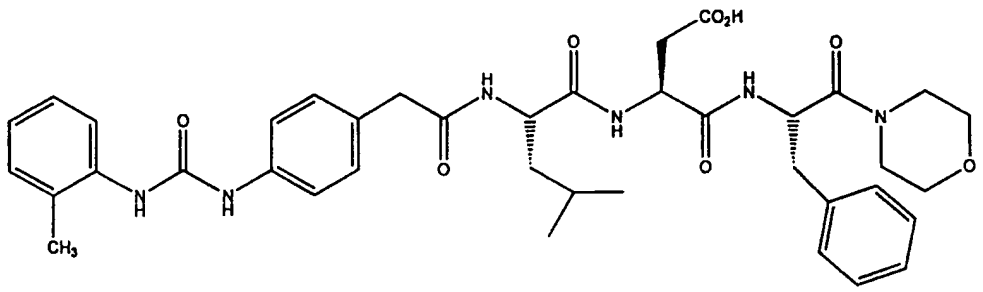
Optimum compounds also occur when R^9 is the 6-membered non-heterocyclic aromatic, partially saturated or saturated ring or the 6-membered heterocyclic aromatic ring containing from 1 to 3 nitrogen atoms, or the 3-indolyl ring as described above.

Compounds containing A as the nitrogen atom and R^{10} taken together with R^{11} to form a ring structure as described above also are optimum.

In addition, compounds containing R^{12} as a primary carboxamide group and the chiral carbon atom is in the R form are optimum.

The following are exemplary compounds of Formula 1.

(14)



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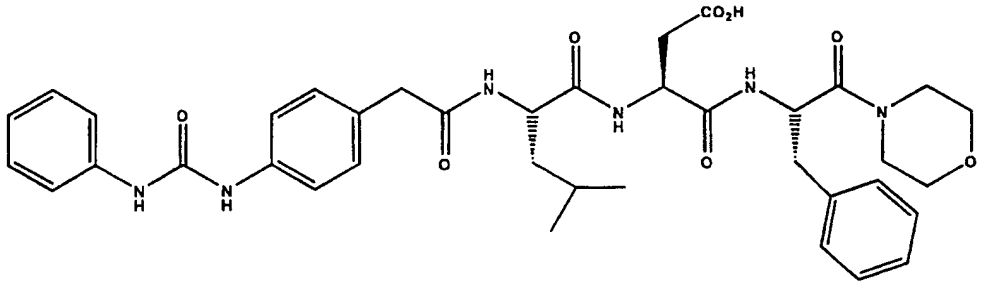

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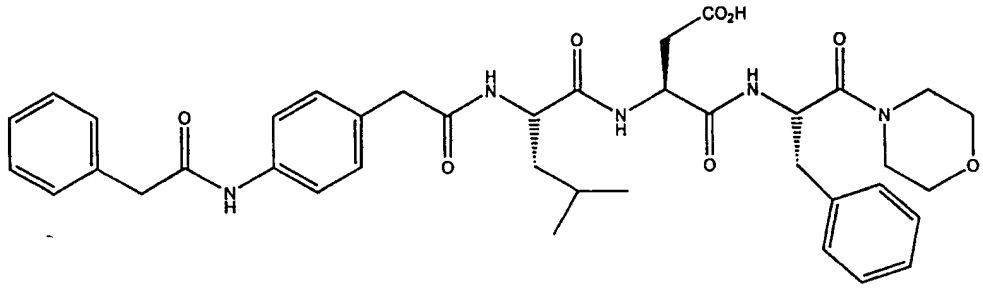

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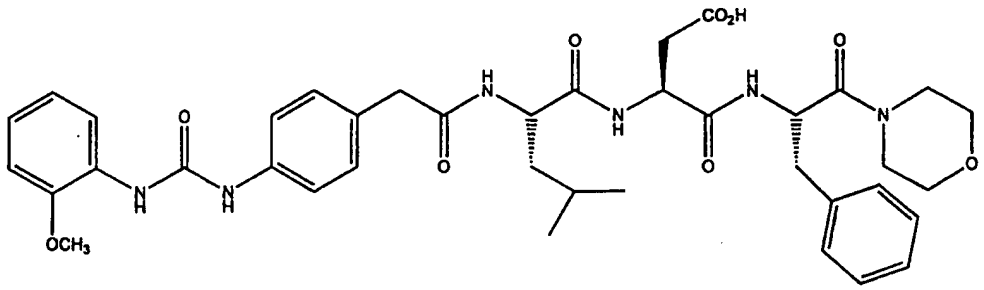

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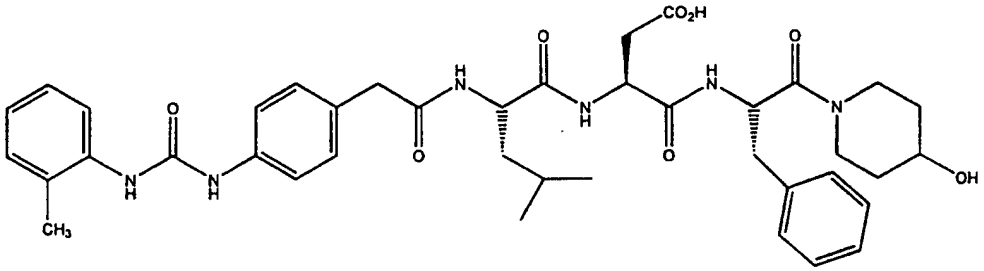

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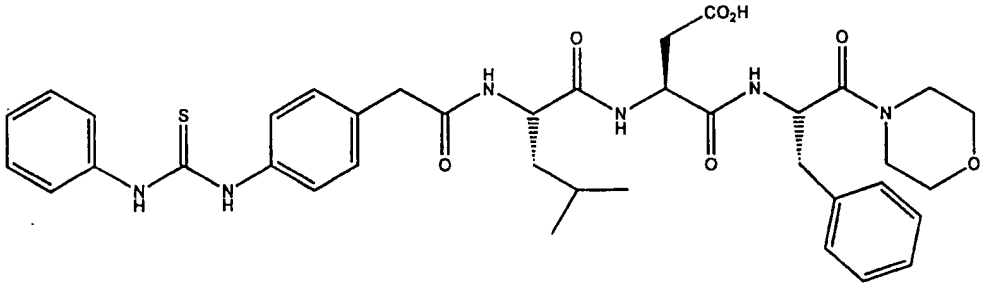

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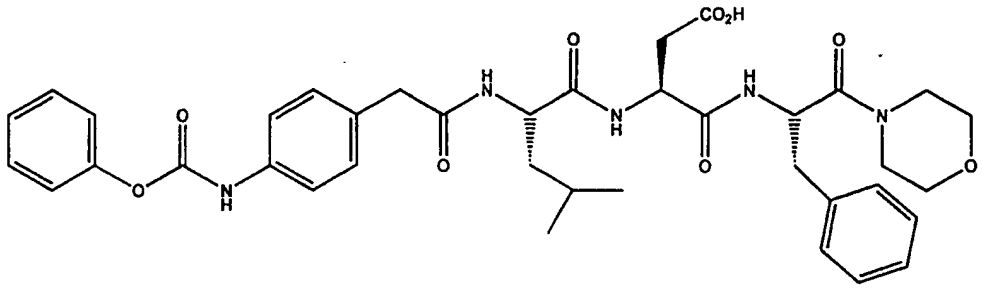

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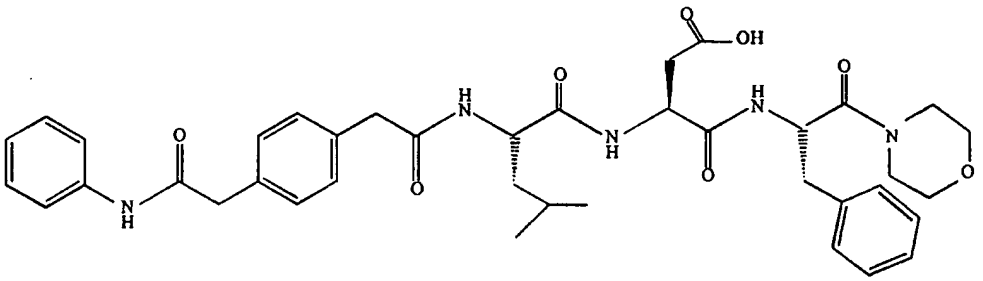

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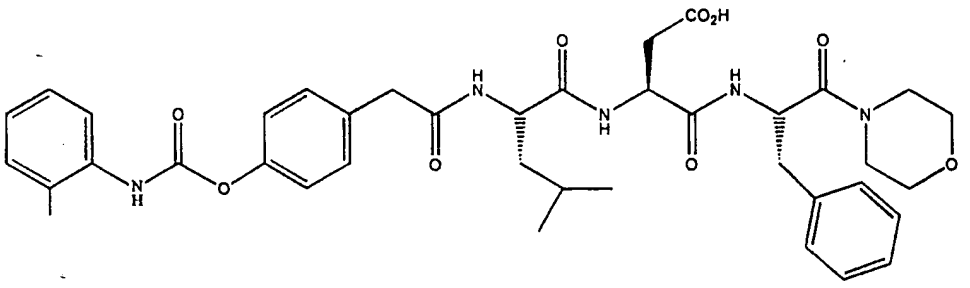

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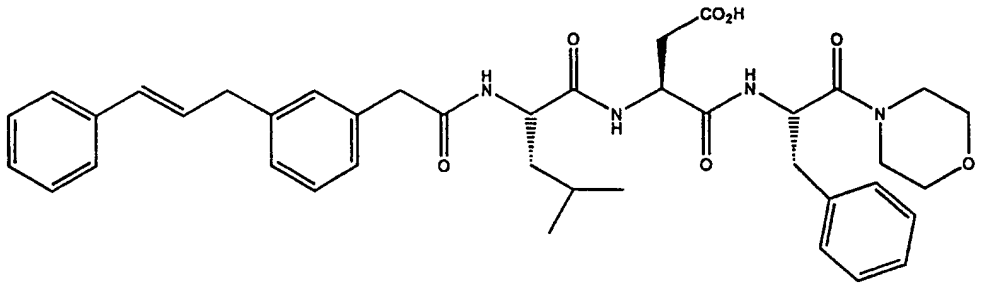

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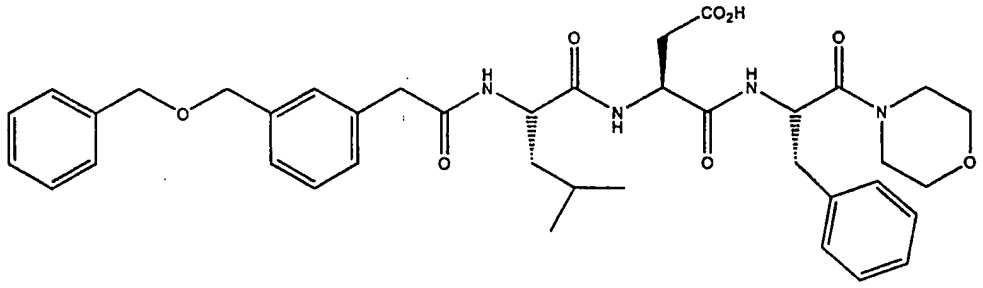

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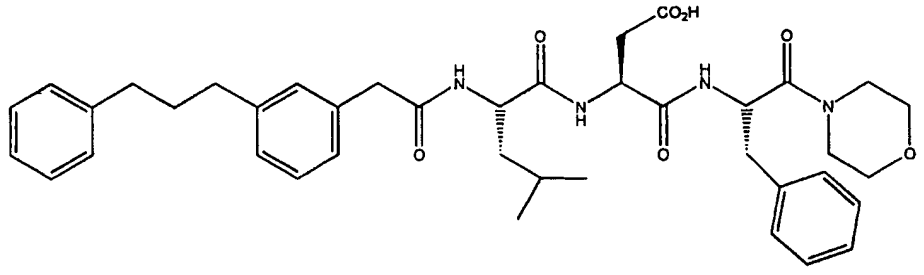

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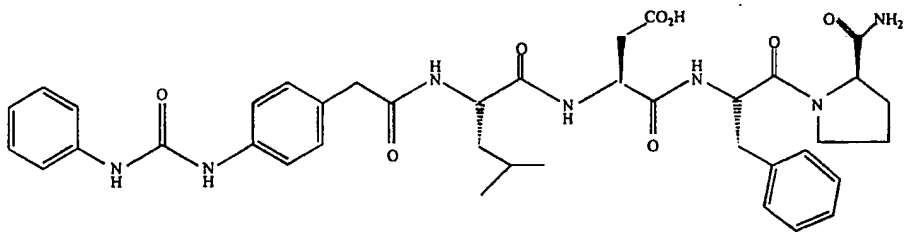

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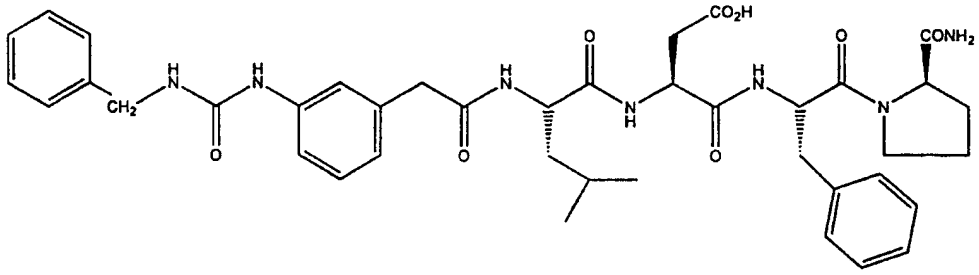

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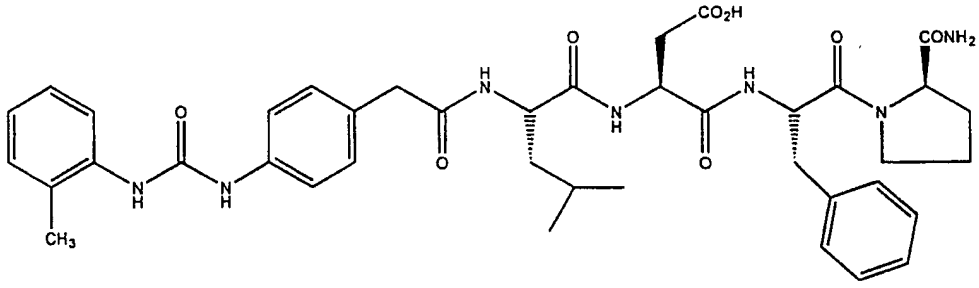

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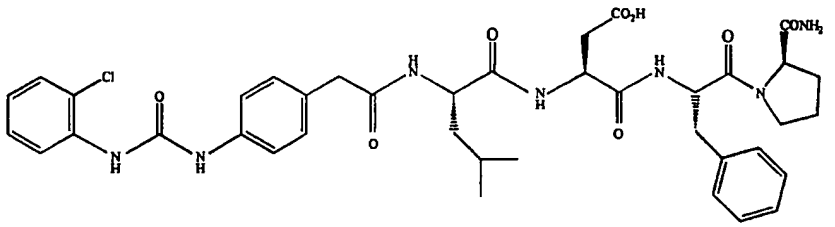

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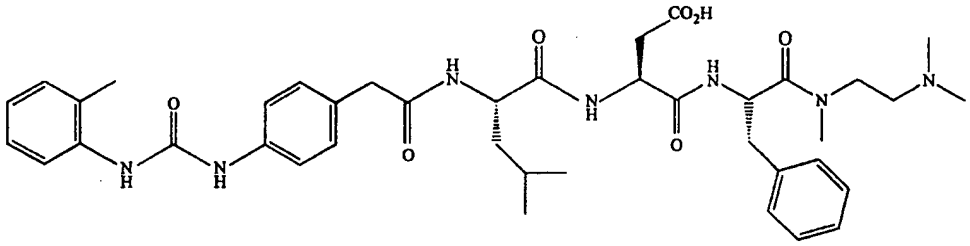

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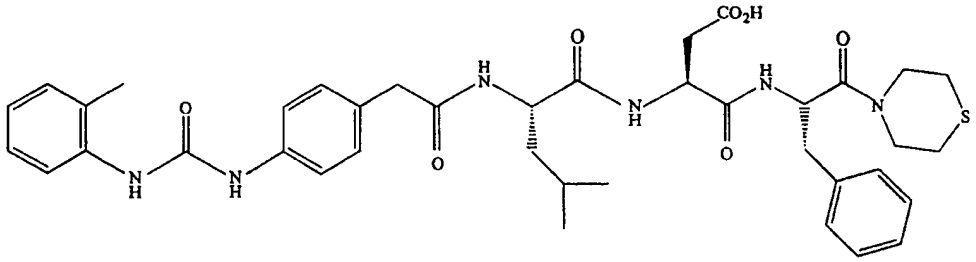

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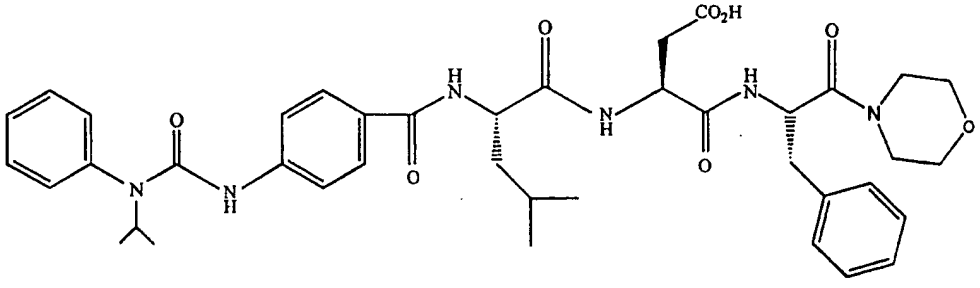

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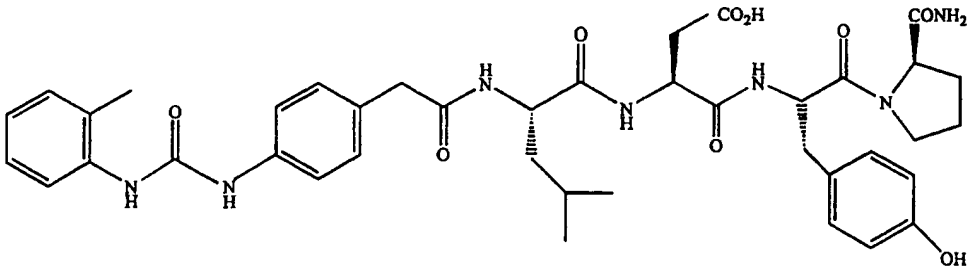

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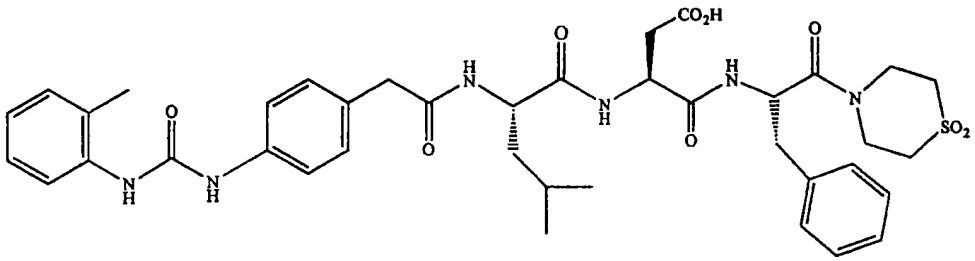

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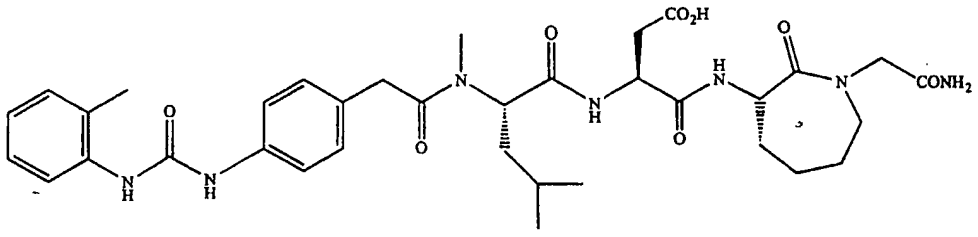

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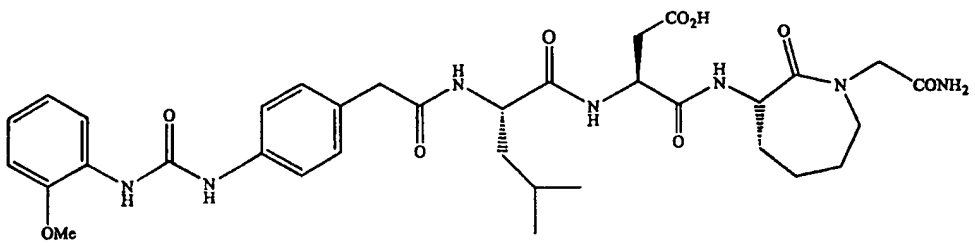

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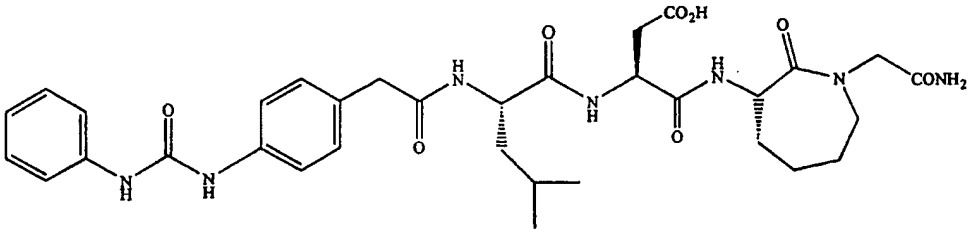

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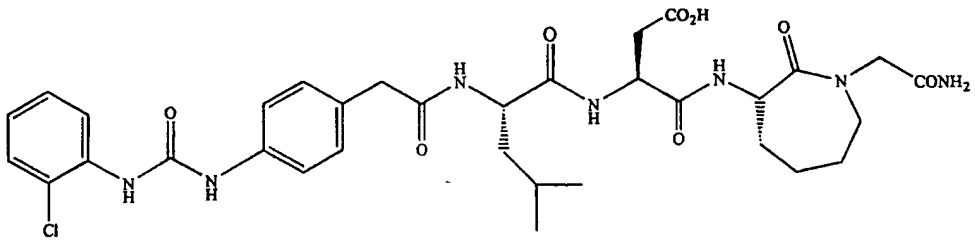

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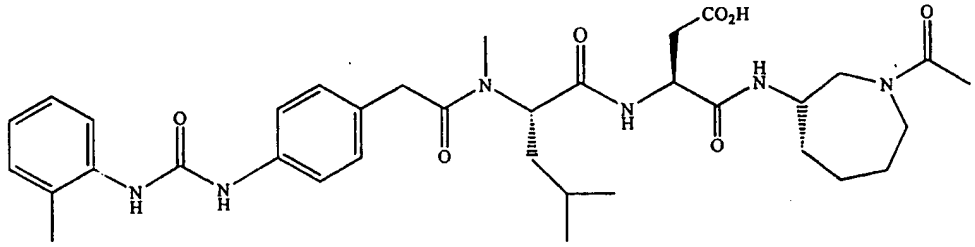

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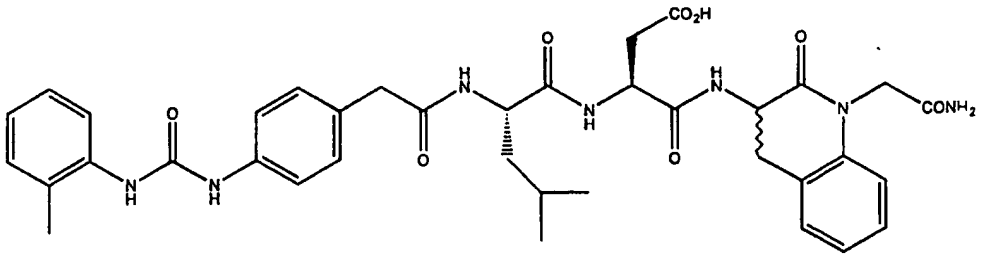

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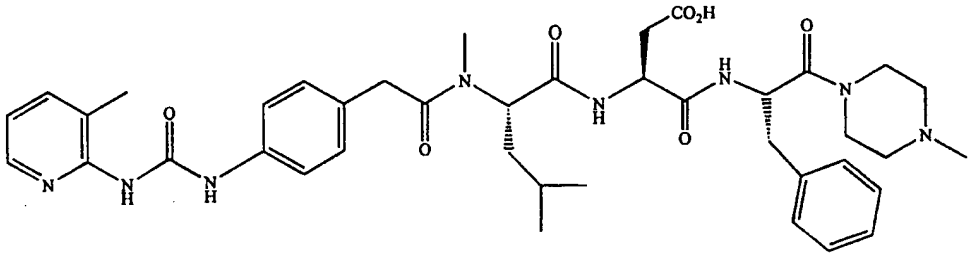

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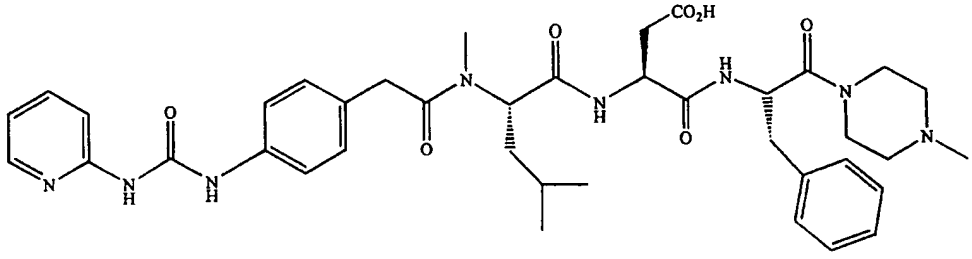

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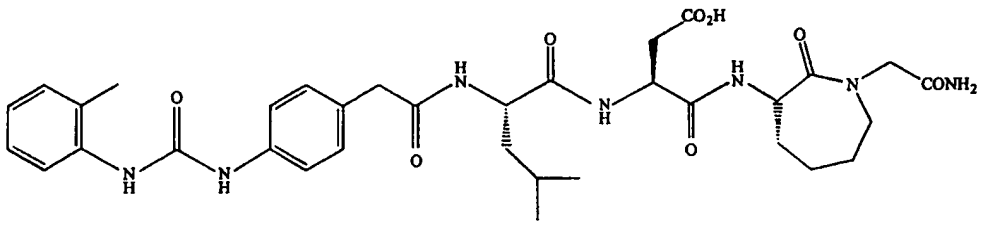

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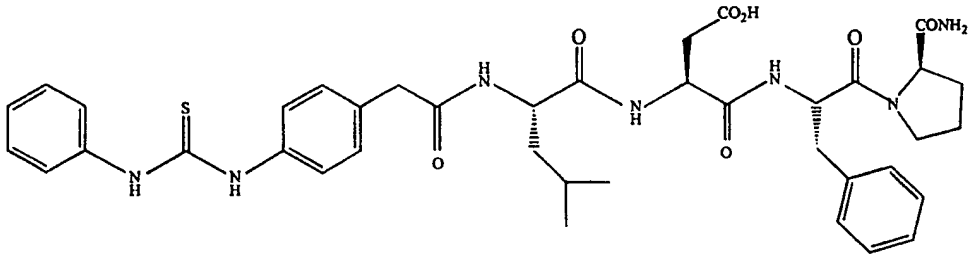

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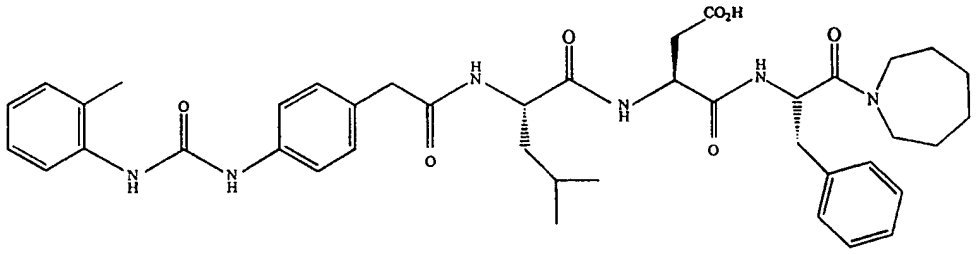

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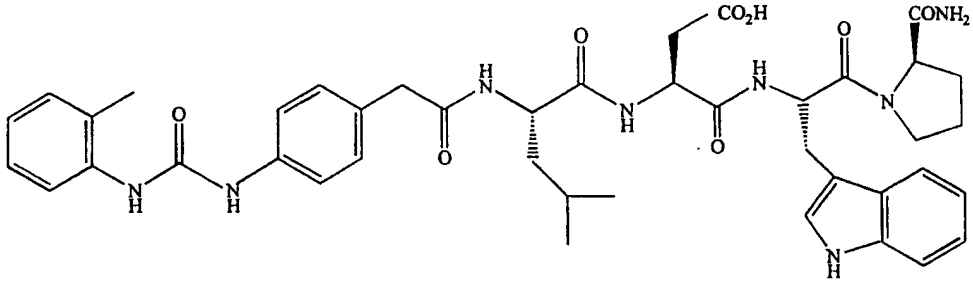

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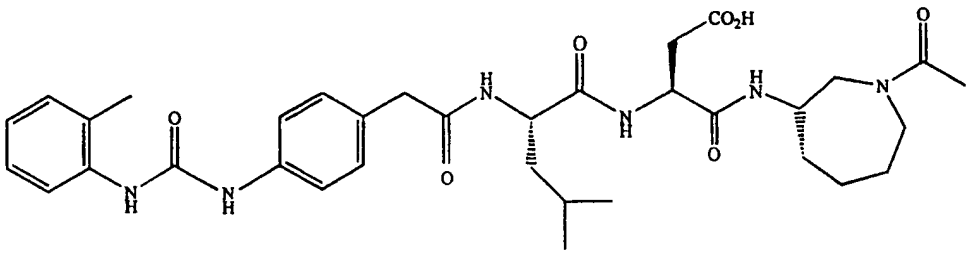

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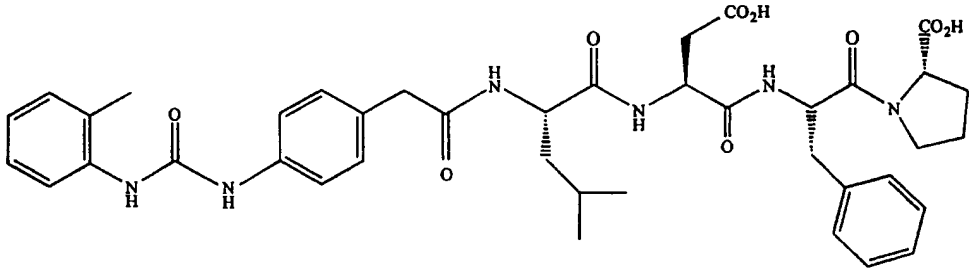

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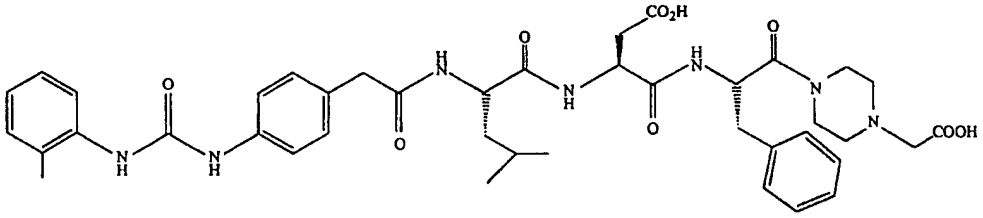

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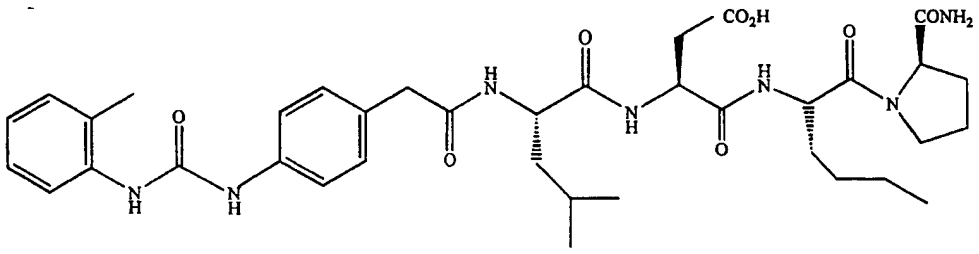

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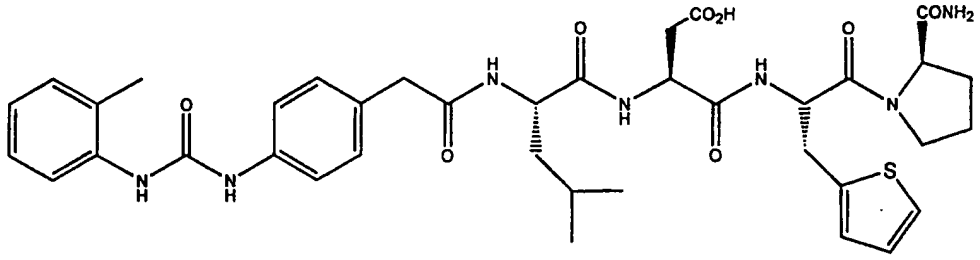

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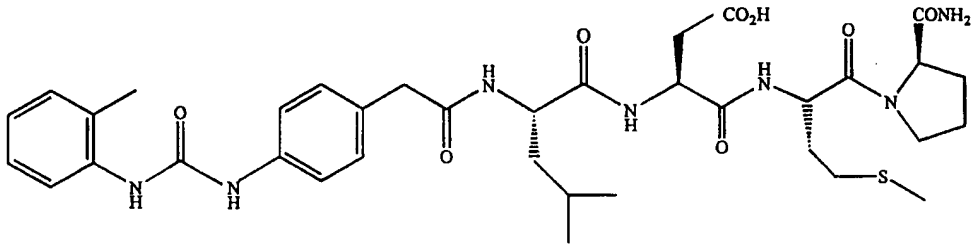

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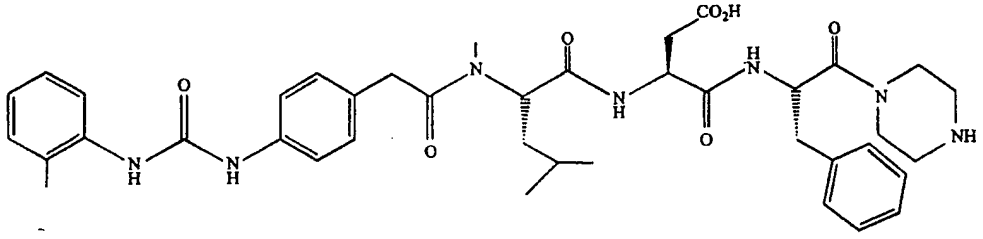

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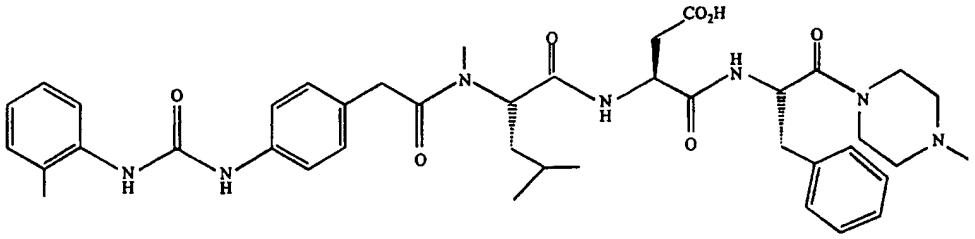

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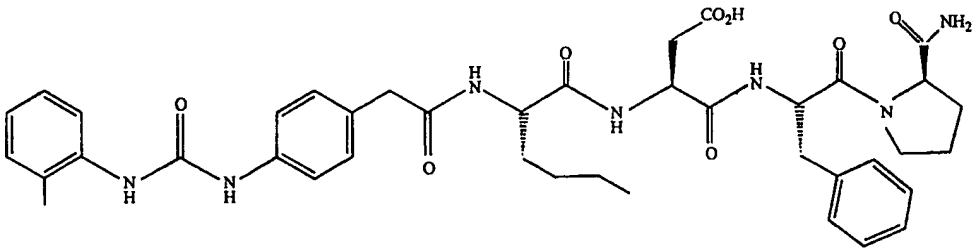

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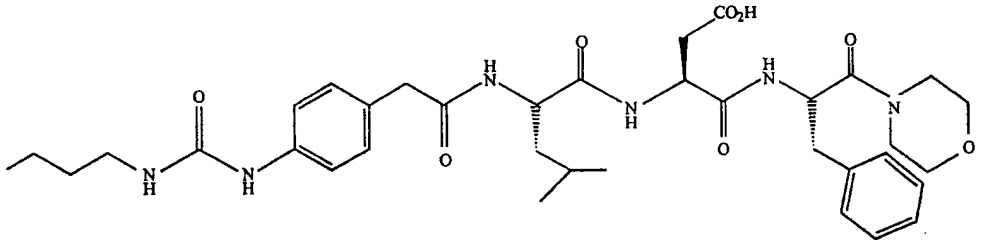

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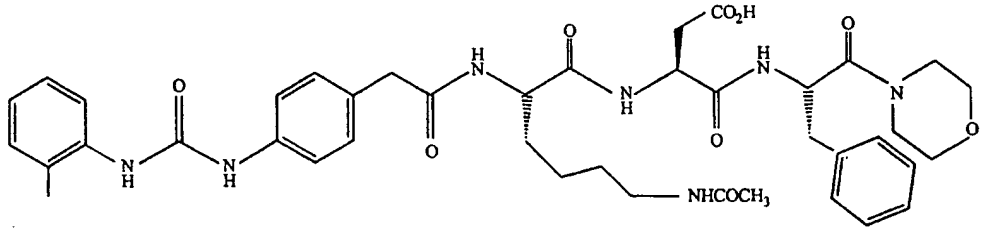

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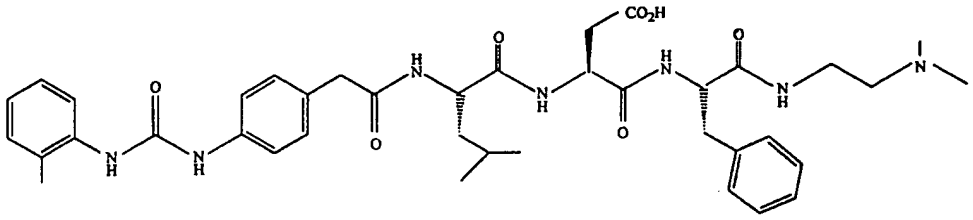

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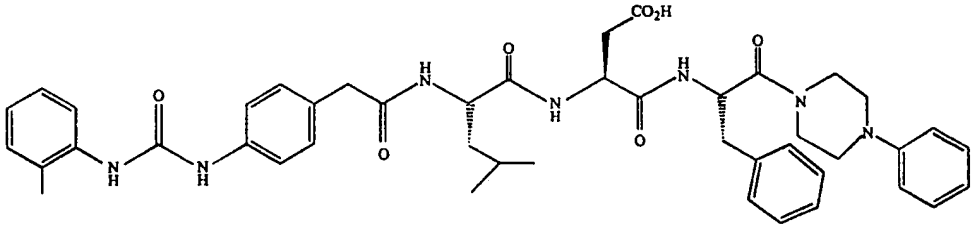

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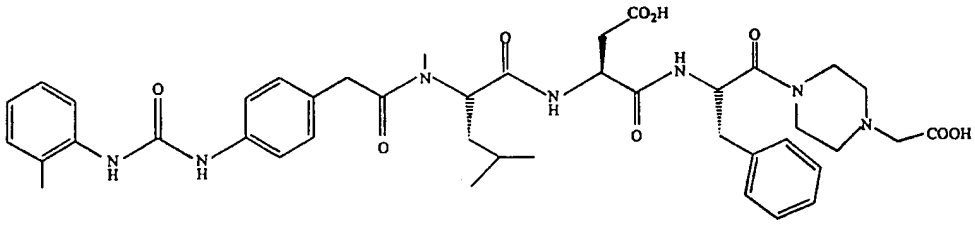

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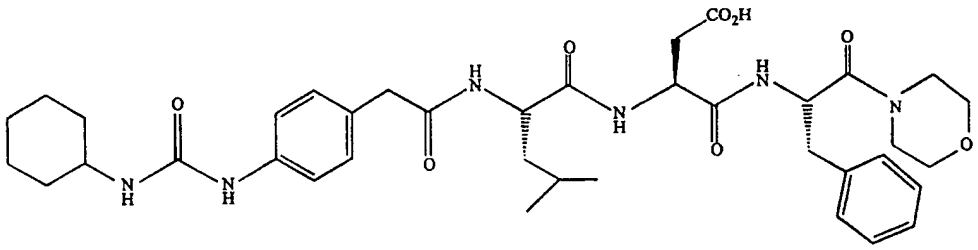

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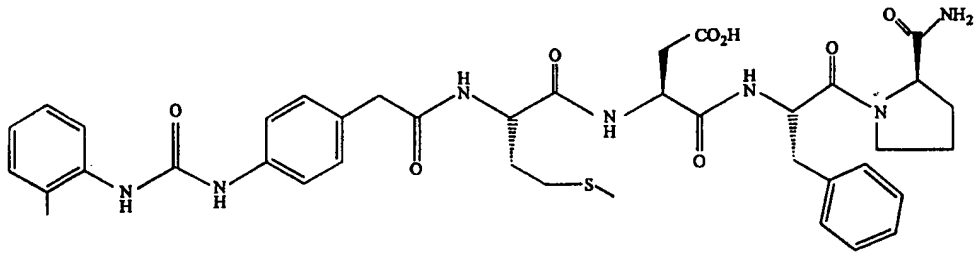

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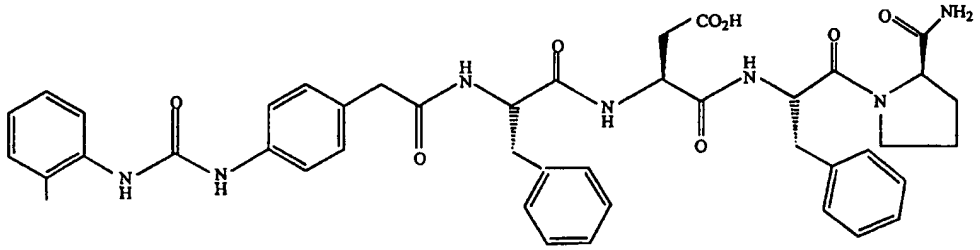

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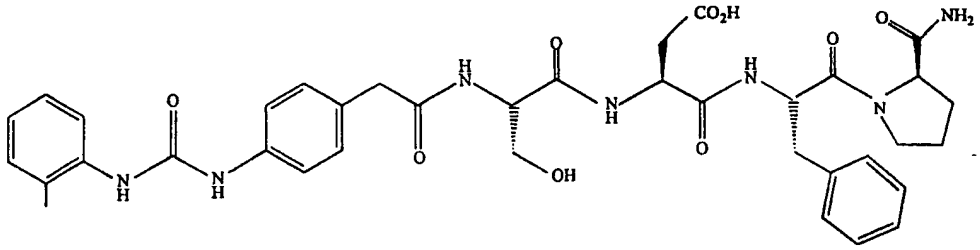

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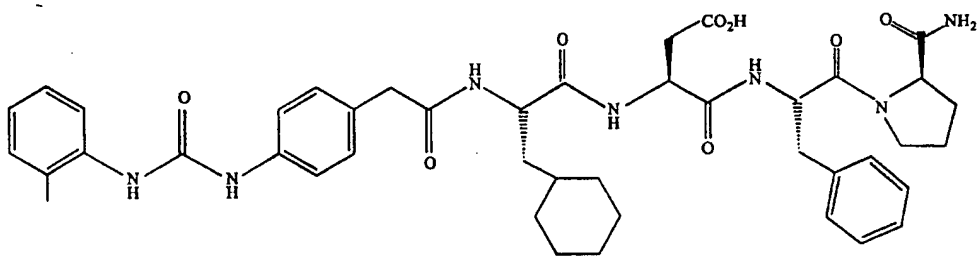

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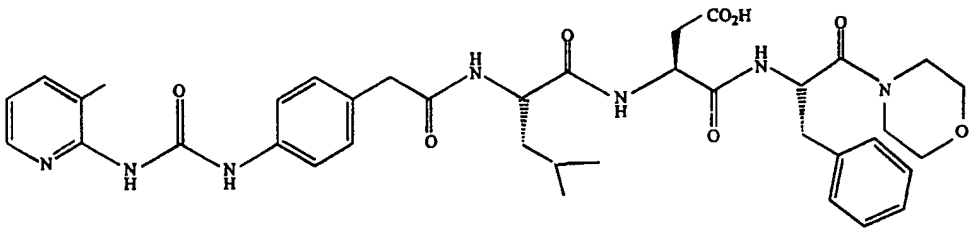

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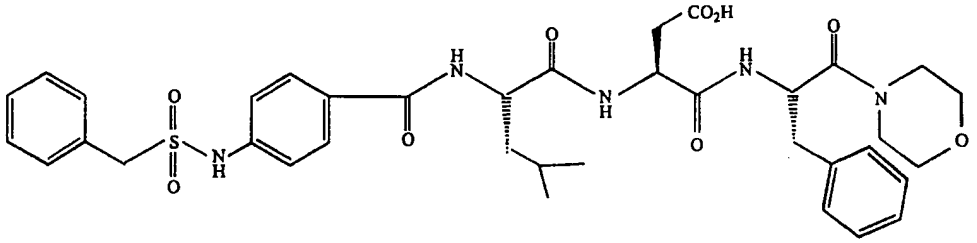

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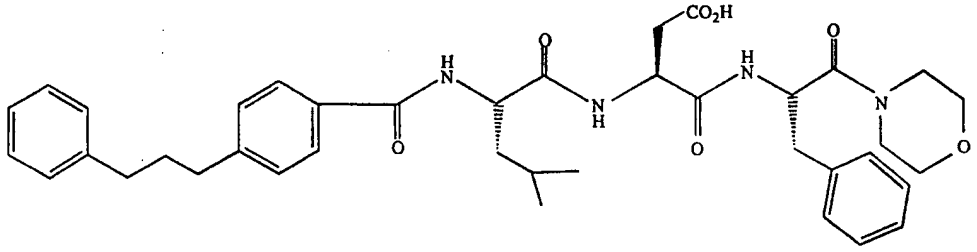

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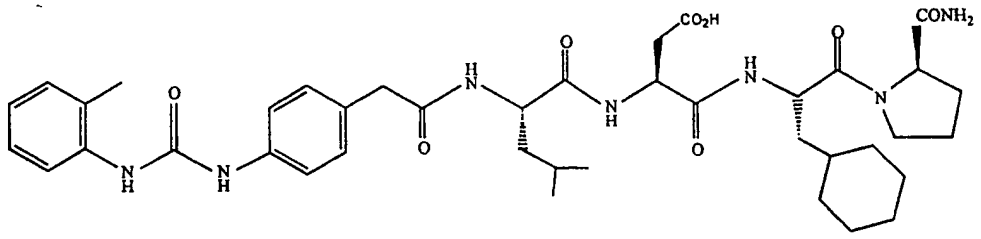

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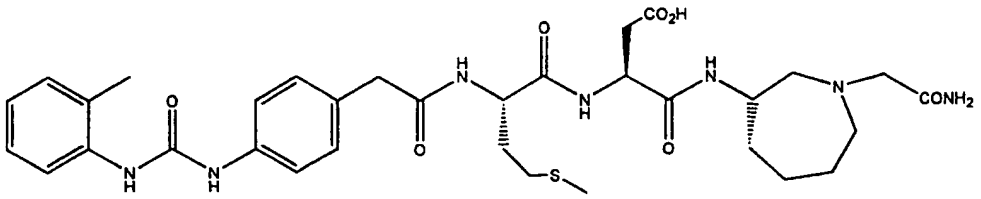

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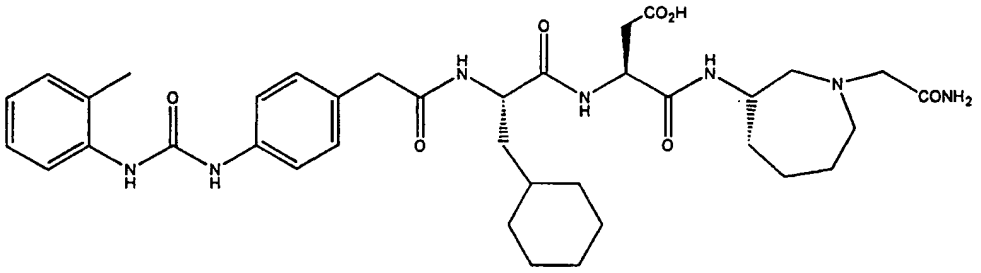

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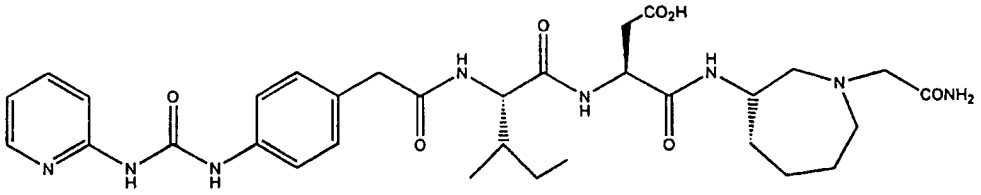

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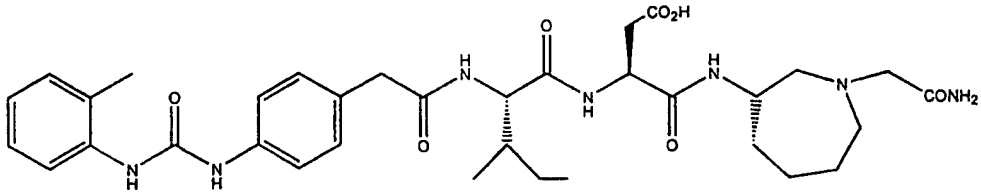

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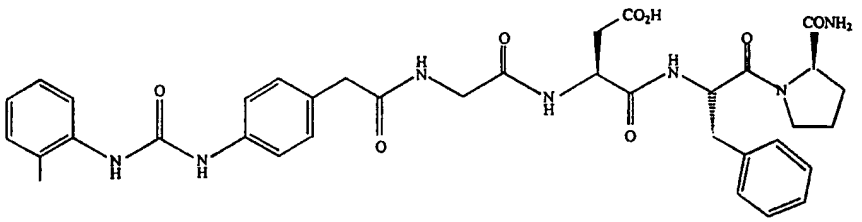

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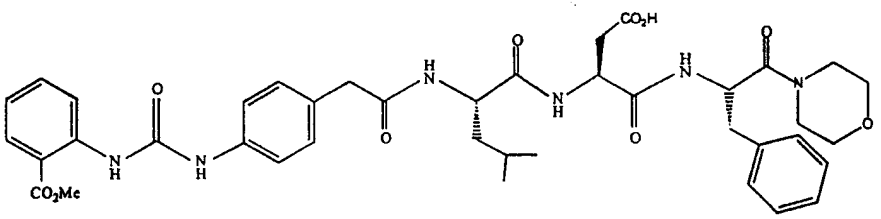

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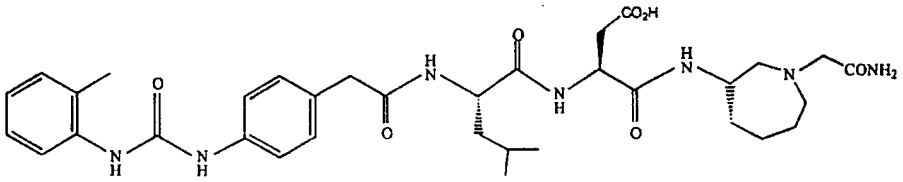

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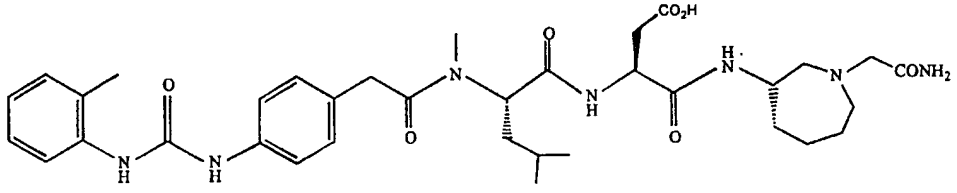

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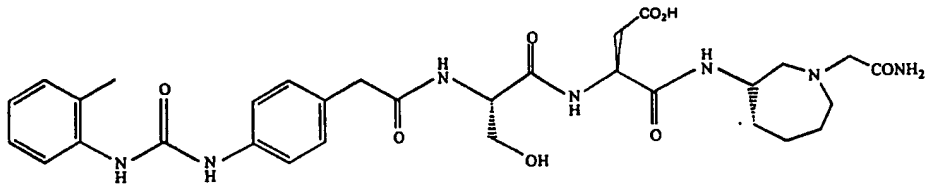

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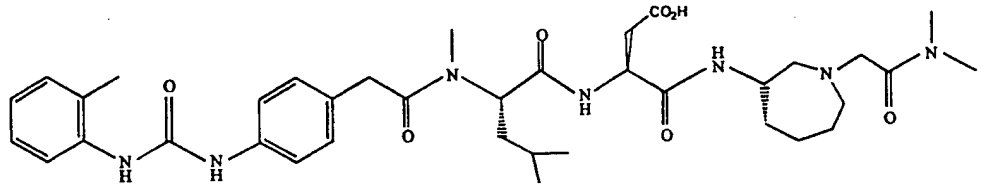


The invention further encompasses a group of compounds using any combination of the substituents at R^1, R^2, R^3, R^4, and R^6 set forth above in compounds of the Formulas (14) through (79).

The invention also encompasses a compound selected from the group of compounds consisting of the Formulas (35), (43), (71), (76), (77), (78), and (79).

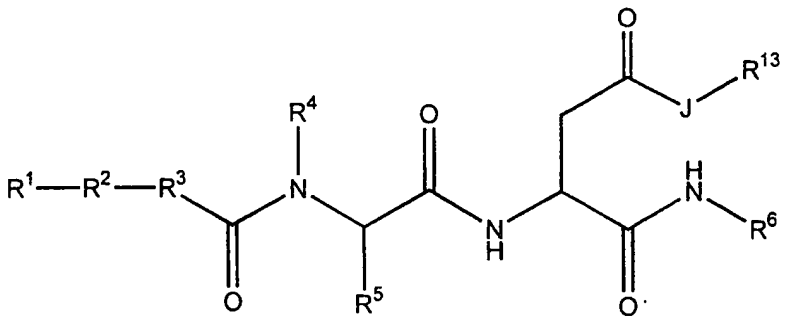
The invention is also directed to a pharmaceutically acceptable derivative of the compound of Formula 1. A pharmaceutically acceptable derivative is a compound of Formula 1 to which a chemical group is attached that facilitates the use of the compound *in vitro* or *in vivo*. Such prophylactic or pharmaceutical derivatives include compounds that inhibit VLA-4 binding after *in vivo* processing. Such derivatives can

be enzymatically or hydrolytically cleaved *in vivo* to liberate a compound that inhibits VLA-4 binding.

A pharmaceutically acceptable derivative also includes a derivative of a compound of Formula 1 that improves the water-solubility, bioavailability or oral availability of the compound. Such a derivative can, but does not have to be, *in vivo* processed for improved water-solubility, bioavailability or oral availability.

Thus, the invention is directed to a pharmaceutically acceptable derivative having the following Formula (80):

(80)



In Formula 80, J is an oxygen or a sulfur atom. Furthermore, R^{13} is:

a) a lower cyclohexyl alkyl that is optionally substituted by a hydroxyl, phenyl, phenyl sulfonyl, pyridinyl, pyridinyl N-oxide, a (lower alkyl) amino, a di(lower alkyl) amino, a (lower alkyl) amide, a di(lower alkyl) amide, a di(lower alkyl)sulfide, a (lower alkoxy)lower alkyl, a ((lower alkoxy)lower alkoxy)lower alkyl, a (((lower alkoxy) lower alkoxy)

lower alkoxy) lower alkyl, a (lower alkylcarbonyloxy)lower alkyl, (N-(lower alkyl)aminocarbonyl)lower alkyl, a ((N-(lower alkyl))(N-(lower alkoxy))aminocarbonyl)-lower alkyl, a (N,N'-di(lower alkyl)aminocarbonyl)lower alkyl, a (N'-morpholinocarbonyl)lower alkyl, (benzyloxycarbonyl)methyl, a 1-((O-((lower alkylcarbonato))eth-1-yl group;

b) a 2-oxo-1,3-dioxolen-4-ylmethyl; or

c) a cyclohexyl, a phenyl, a pyridinyl, a pridinyl N-oxide, a 1,3- dioxan-2-yl, a 3-tetrahydropyranyl, a (4-hydroxybutyric)lacton-3-yl, or a phthalidyl ring, wherein said ring is connected to J either directly by a bond or indirectly by a lower alkyl group.

R^1, R^2, R^3, R^4, R^5 and R^6 in Formula 80 are as in Formula 1 above.

A "lower alkyl," a "(lower alkyl) amino", a "di(lower alkyl) amino," a "di(lower alkyl)sulfide," and "(lower alkoxy)lower alkyl" group in Formula 80 are as defined above.

A "(lower alkyl) amide" group in Formula 80 is a lower alkyl radical bonded to the nitrogen atom of an amide radical and denotes radicals such as methyl amide (CH_3NCO-) t-butyl amicle and the like.

A "di(lower alkyl) amide" group means two lower alkyl radicals bonded to the nitrogen atom of an amide radical. The lower alkyl groups can be the same or different. The term denots groups such as dimethyl amide ($(CH_3)_2$ NCO-), (t-butyl) n-propyl amide and the like.

A "((lower alkoxy)lower alkoxy)lower alkyl" group is a lower alkoxy radical bonded to a lower alkoxy radical which is bonded to a lower alkyl radical. The term denotes groups such as methoxymethoxymethyl ($CH_3OCH_2OCH_2$-), 3(2'(ethoxy)ethoxy)propyl, and the like.

A "(((lower alkoxy)lower alkoxy) lower alkoxy) lower alkyl" group is a lower alkoxy radical bonded to a lower alkoxy radical which is bonded to another lower alkoxy radical which is bonded to a lower alkyl radical. The term denotes groups such as methoxymethoxymethoxymethyl ($CH_3OCH_2OCH_2OCH_2$-), 3((2'(ethoxy)2'ethoxy)ethoxy) propyl and the like.

A "(lower alkylcarbonyloxy)lower alkyl" group is a lower alkyl group bonded to a carbonyl group of an ester radical bound to a lower alkyl radical and exemplified by such groups as methylcarbonyloxymethyl (CH_3COOCH_2-), pivaloyloxyethyl, and the like.

The group, "(N-(lower alkyl)aminocarbonyl)lower alkyl," contains a lower alkyl radical bonded to an amino radical which is bonded to the carbon of a carbonyl radical which is bonded to a lower alkyl radical. The term denotes groups such as methylaminocarbonylmethyl ($CH_3NHCOCH_2$-), 3-(4'(n-butylaminocarbonyl))n-propyl and the like.

By the term "((N-(lower alkyl))(N-(lower alkoxy))aminocarbonyl)-lower alkyl" is meant a lower alkyl radical and a lower alkoxy radical bonded to an amino radical which is bonded to a carbonyl radical and denotes groups such as N-methyl-N-methoxyaminocarbonylmethyl ($CH_3(CH_3O)NCOCH_2$-), N-(n-but-4-yl)-N-(ethoxy)

aminocarbonylethyl and the like.

The related term "(N,N'-di(lower alkyl)aminocarbonyl)lower alkyl" is defined as two lower alkyl radicals bonded to an amino radical which is bond to a carbonyl radical which is bonded to a lower alkyl radical. The term denotes such groups as N-methyl-N-ethylaminocarbonylmethyl ($CH_3(CH_3CH_2)NCOCH_2$-), N(n-but-4-yl)-N-(n-prop-3-yl))aminocarbonylmethyl, and the like.

A "(N-morpholinocarbonyl)lower alkyl" group is a morpholinyl radical bonded by the nitrogen atom of the morpholino group to the carbon atom of the carbonyl which is bonded to a lower alkyl radical. The term denotes groups such as (N'-morpholinocarbonyl)methyl, 3(N'-morpholinocarbonyl)n-butyl, and the like.

A 1-((O-((lower alkylcarbonato))eth-1-yl is a lower alkyl radical bonded to one of the two ether oxygens of a carbonate group, the ethereal oxygen of which is bound to Formula 80.

A "2-oxo-1,3-dioxolen-4-ylmethyl" group includes, for example, 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, 5-phenyl-2-oxo-1,3-dioxolen-4-ylmethyl, and the like.

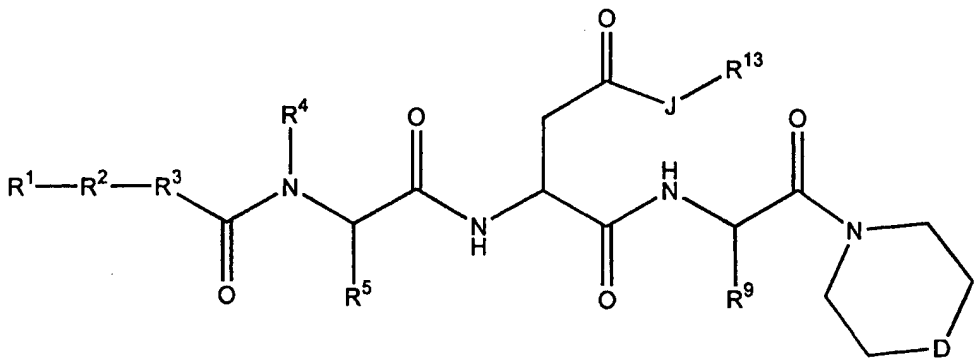
A "phthalidyl" ring includes 3-phthalidyl, or 5,6-dimethylphthalidyl rings.

A pharmaceutically-acceptable derivative of Formula 80 includes a pharmaceutically-acceptable salt of such derivatives. All chiral carbon centers of a Formula 89 compound can be in in a pure R form, pure S form, or a mixture of R and S forms in any proportion.

A compound of Formula 80 also includes a bioisostere of the compound of Formula 80.

A group of pharmaceutically-acceptable derivatives of note within Formula 80 has the following Formula (81):

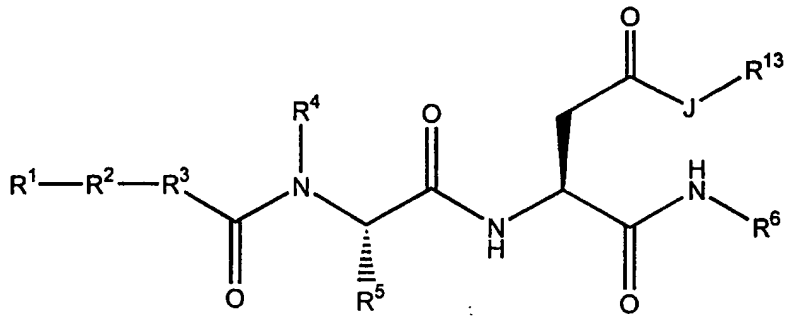
(81)



In Formula 81, J, R^1, R^2, R^3, R^4, R^5 and R^{13} are as in Formula 80 above. D and R^9 in Formula 81 are as in Formula 9 above.

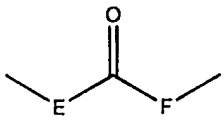
A group of optimum compounds with the compounds of Formula 80 has the following Formula (82):

(82)



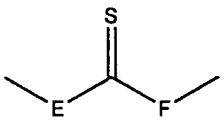
In Formula 82, J, R^1, R^2, R^3, R^4, R^5, R^6 and R^{13} are as in Formula 80 above.

A group of optimum compounds of Formula 80 has an R^2 which is a group of the Formula (2):



(2)

or of the Formula (3):



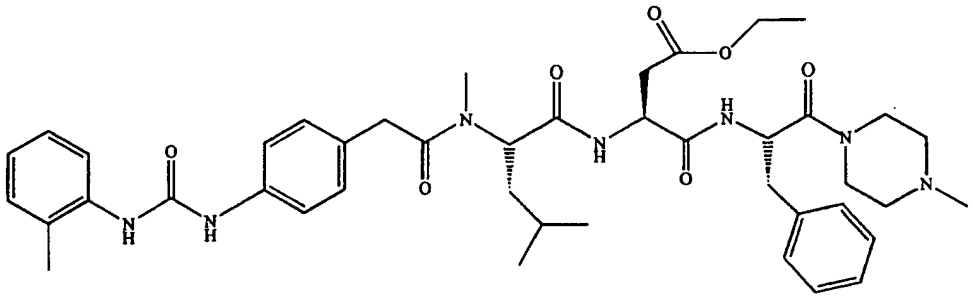
(3)

and E is a CX^1X^2 group, a NX^3 group or an oxygen atom and F is a CX^4X^5 group, a NX^6 group or an oxygen atom; and X^1, X^2, X^3, X^4, X^5, and X^6 are

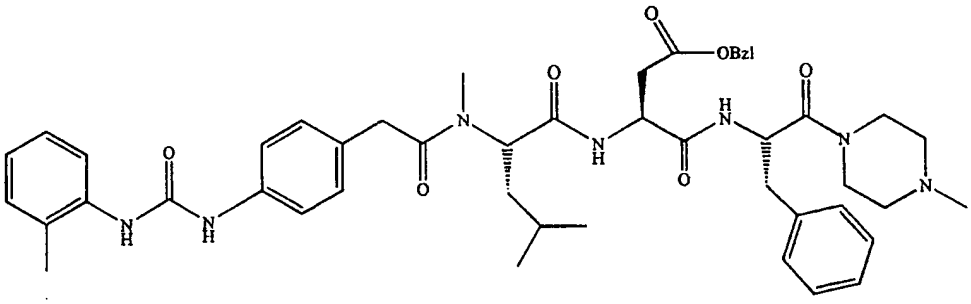
independently selected from the group consisting of a hydrogen atom or a lower alkyl group with the provisios that E and F both are not simultaneously oxygen atoms; and if R^1 is the alkyl group, R^2 must be a group of the Formula (2) or (3).

The folLowing are exemplary compounds of Formula 80.

(83)



(84)



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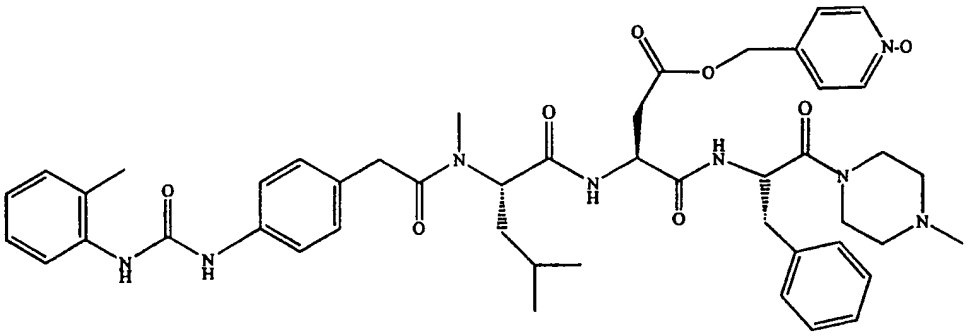

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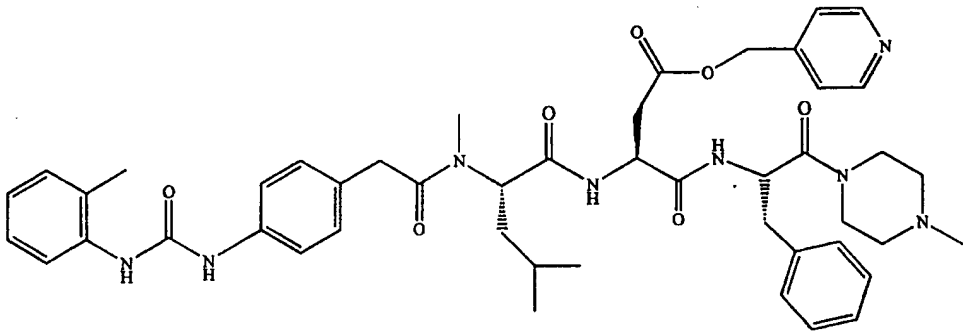

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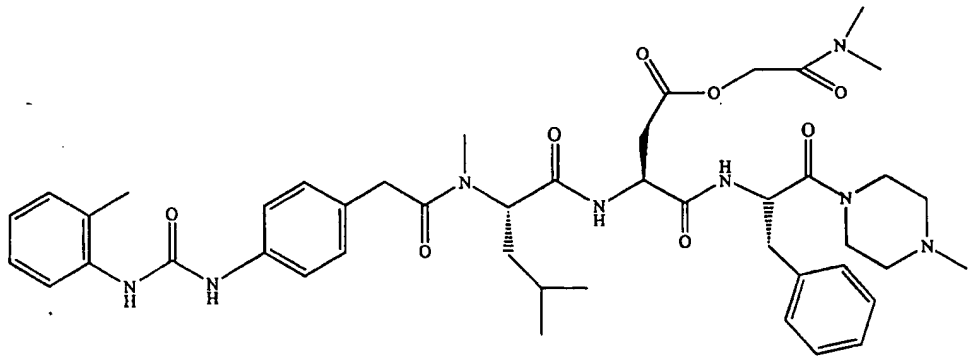
(87)



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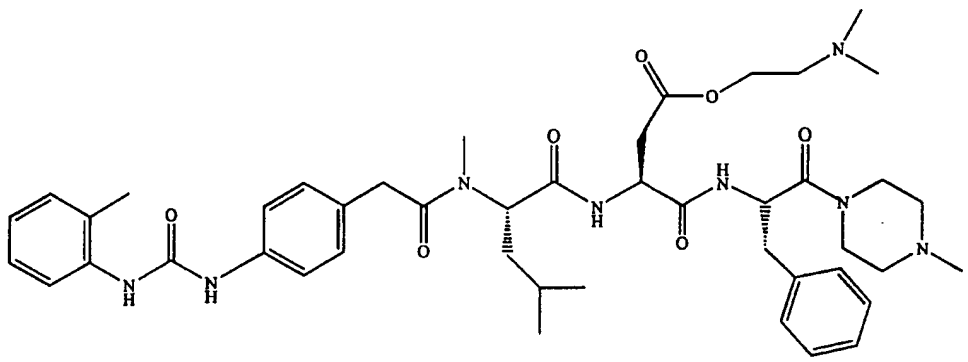
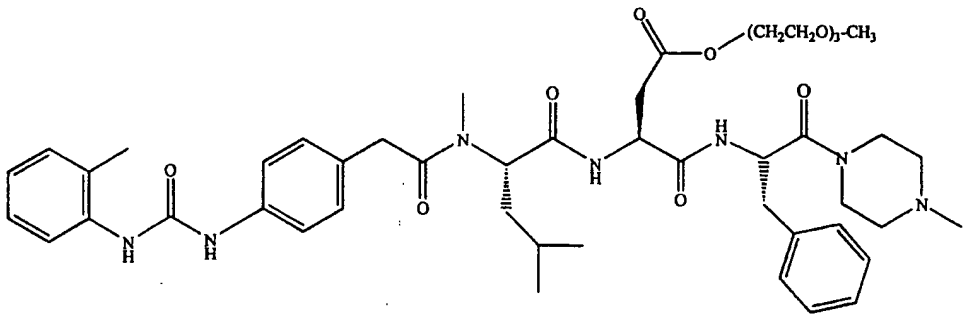


(89)



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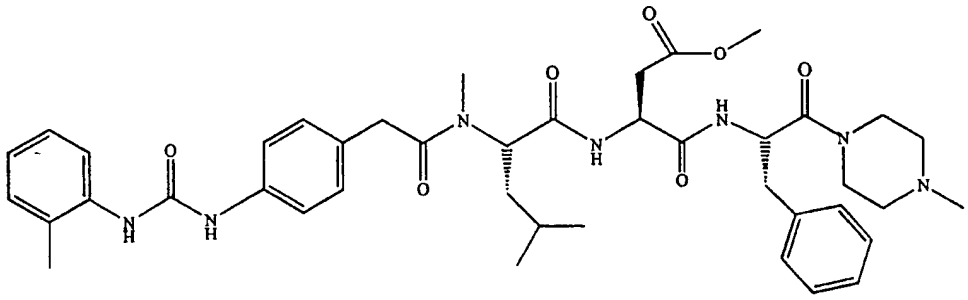

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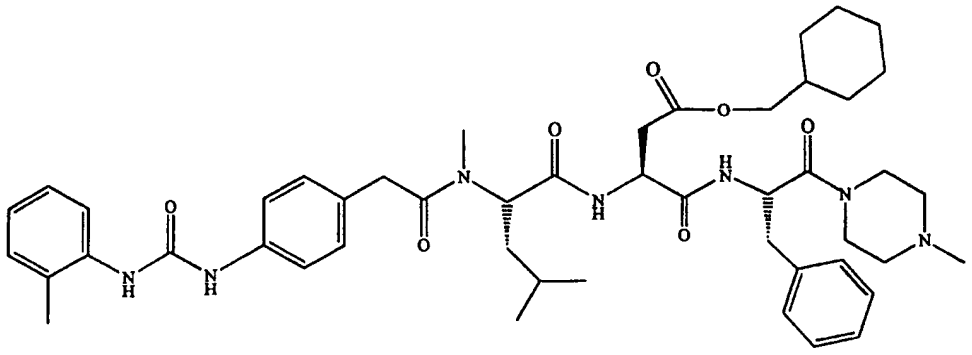

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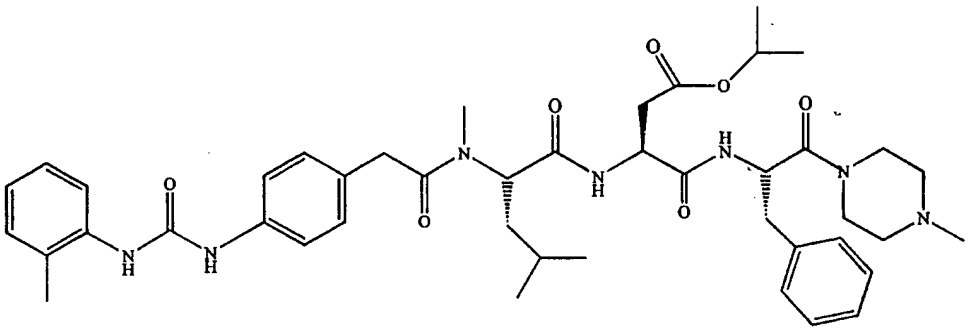

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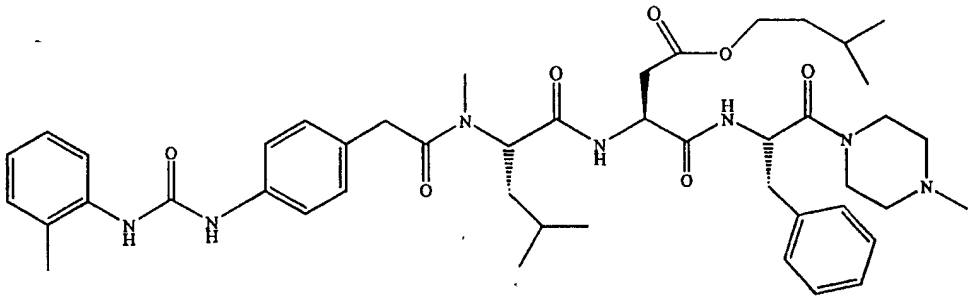

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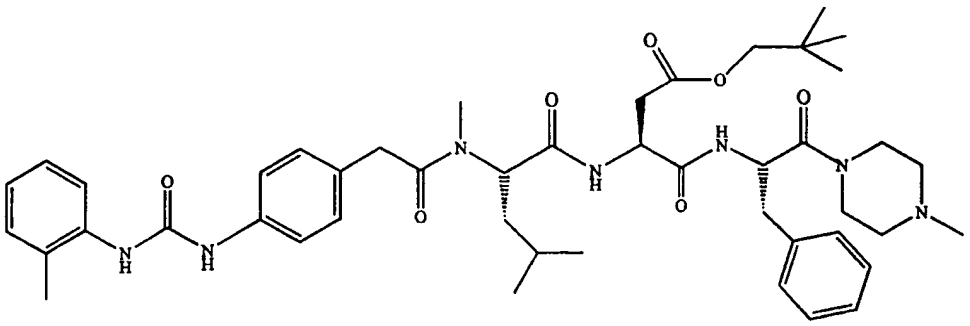
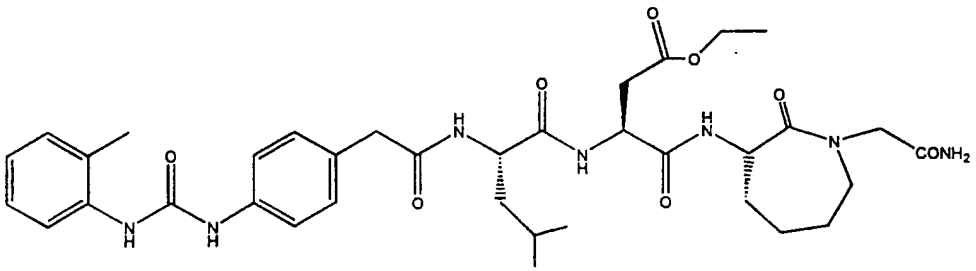
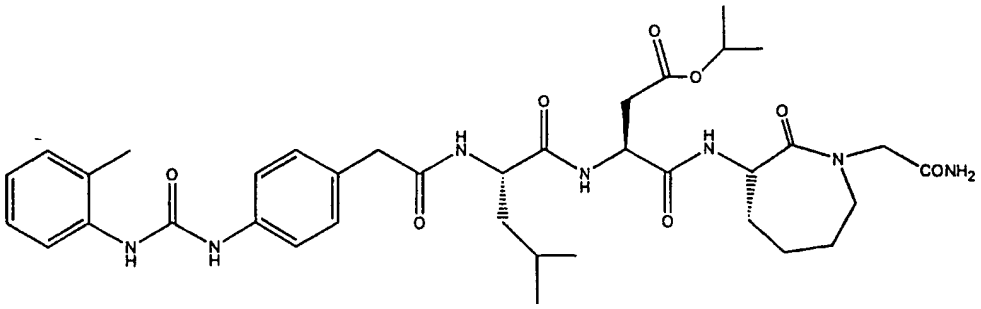


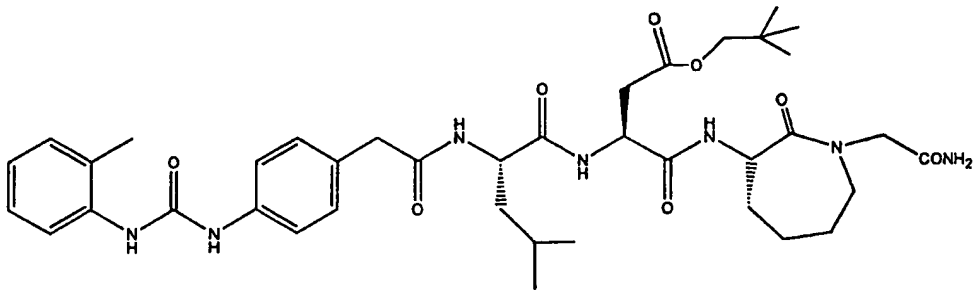
(95)



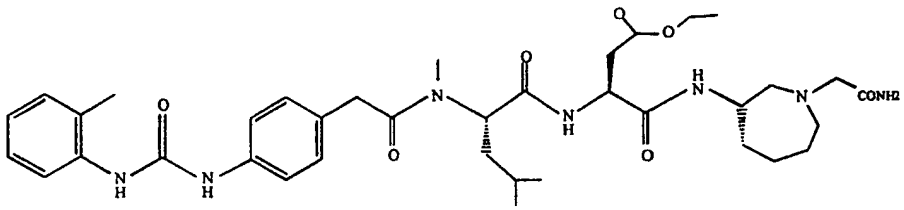
(96)



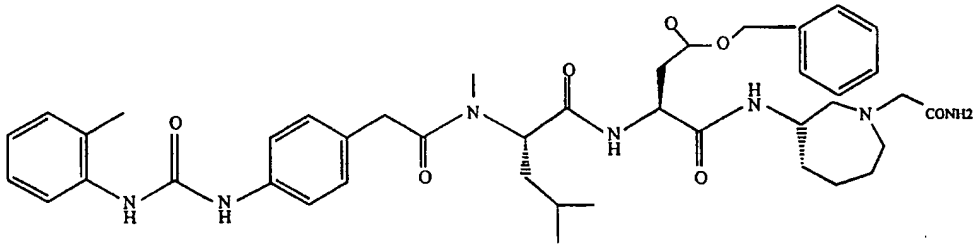
(97)



(98)



(99)

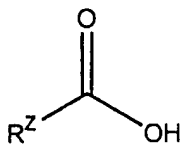


The invention further encompasses a group of pharmaceutical compositions using any combination of the substituents at R^1, R^2, R^3, R^4, R^5, R^6, J, and R^{13} set forth above in the compounds of Formulas (83) through (99).

The invention also encompasses a pharmaceutically-acceptable derivative selected from the group of compounds consisting of the Formulas (95), (96), (97), (98), and (99).

In synthesizing the compounds of Formula 1, the left terminus and the right terminus of the compound may be synthesized prior to coupling them to the remainder of the compound, or after one or both the nascent termini are already in place. By "left terminus" and "right terminus" is meant the R^1-R^2-R^3- group and the -N-R^6 group of Formula 1, respectively.

The left terminus of Formula 1, or its precursor, is added to the precursor molecule using a reagent of the following Formula A:



A

In Formula A above, R^z can be of the formula:

$$R^1\text{-}R^2\text{-}R^3\text{-};\ \text{or}$$

B

$$Y\text{-}R^3\text{-}.$$

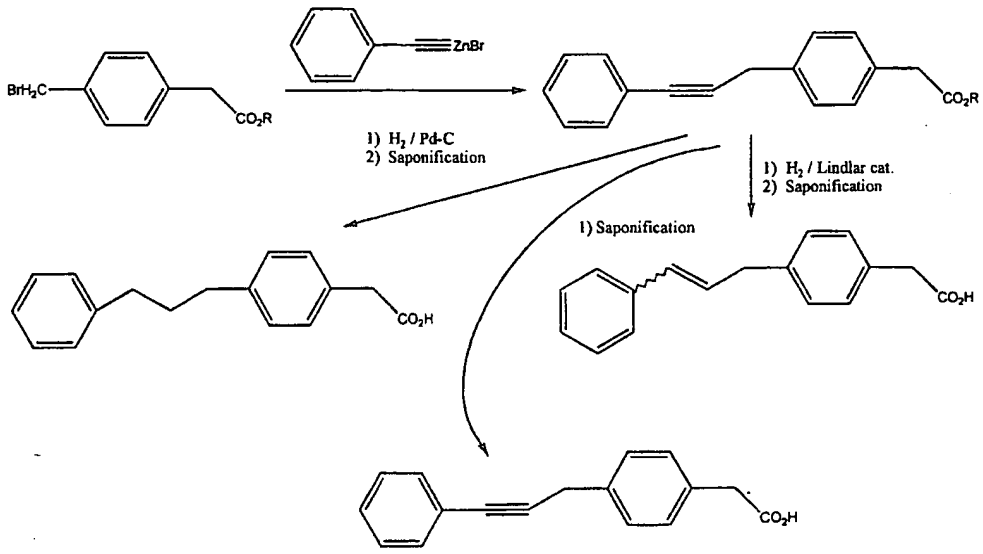
C

Y is a reactive functionality that will eventually become a portion of R^2. When Y is of the

formula Y-R^3-, it can be reacted at any point in the following Schemes 7 through 10 with a reagent of the formula R^1-X, wherein the reaction between X and Y results in the formation of R^2. Thus, Y is a reactive functionality that can be incorporated into R^2. This reactive functionality is, of course, protected at the appropriate stages of the following Schemes 7 through 10.

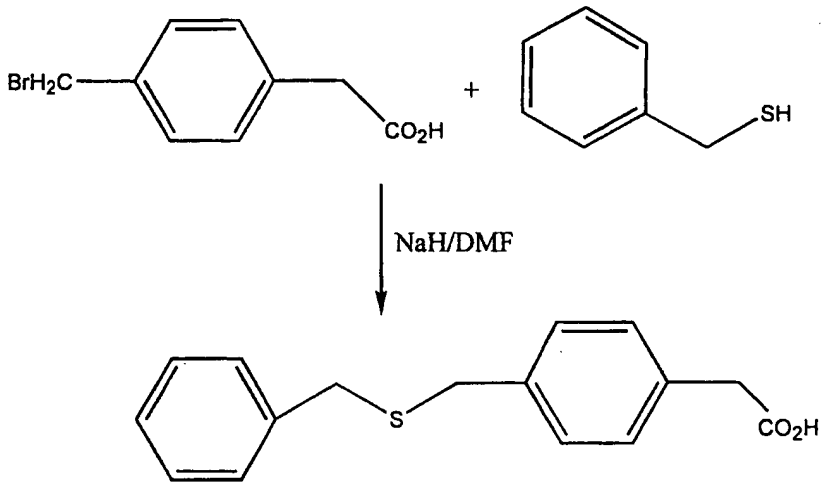
Specific examples of such broader possible synthetic schemes regarding **A** are set forth in the following Schemes 1 through 5, wherein the conversion of R^2 to a group of the formula R^1-R^2-R^3- is completed prior to inclusion in the precursor molecule.

SCHEME 1

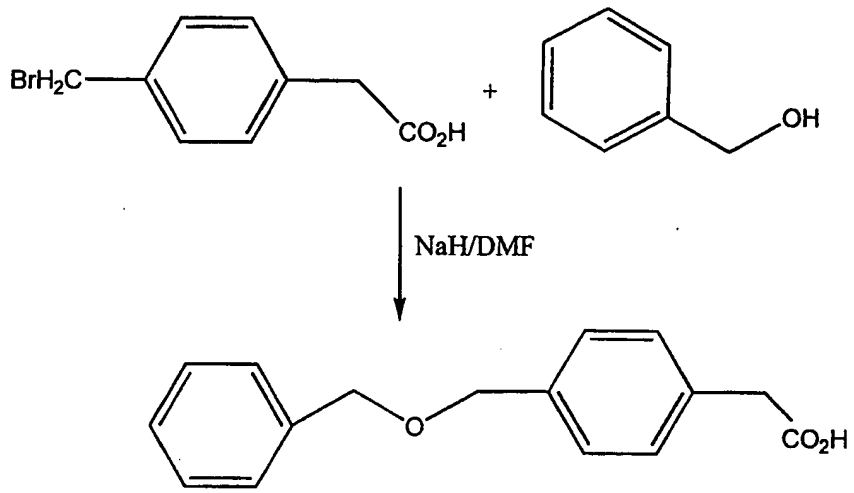


In the above Scheme 1, the "BrH_2C" group of the phenyl acetic acid would represent the "Y" group of an $Y-R^3$ moiety, and the zinc acetylide portion of the organozinc reagent would be the "X" portion of an R^1-X moiety.

SCHEME 2



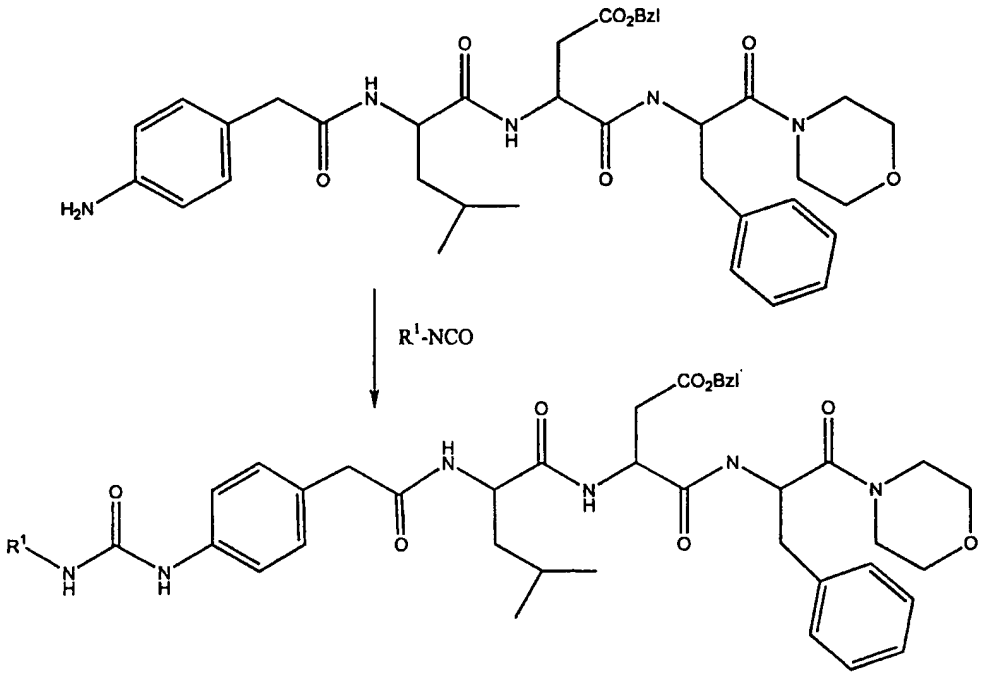
SCHEME 3



In Schemes 2 and 3 above, again the "BrH_2C-" moiety of the substituted phenylacetic acid reagent would be the "Y" portion of the "Y-R^3-" function. Similarly, the hydroxymethylene or thiolmethylene moieties of the benzyl alcohol and benzyl thiol reagents, respectively, represent examples of the "X" portion of the R^1-X reagent.

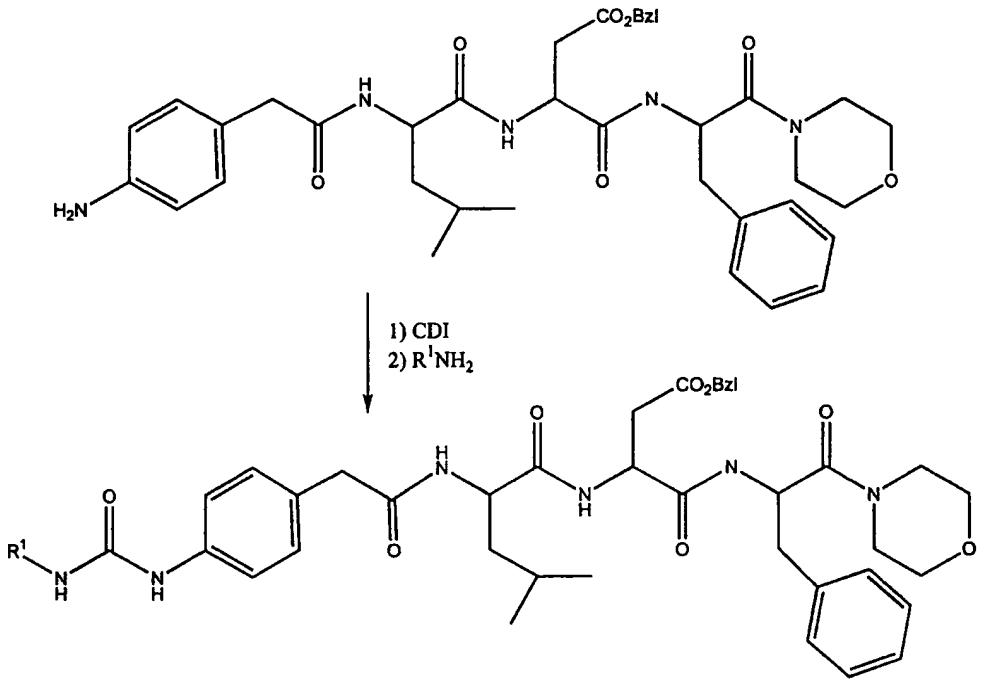
As discussed above, when R^z is of the formula Y-R^3-, the left terminus can be completed after a molecule of Formula **A** (R^z-COOH) has been coupled to the precursor moleucle, as exemplified below in Schemes 4 and 5.

SCHEME 4



In the above Scheme 4, the amino function of the aminophenyl group of the left terminus of the substrate molecule would be the "Y" of a "Y-R^3-" group, and the isocyanate group of the R^1-NCO reagent represents the "X" portion of an "R^1-X" reagent. "Bzl" is a benzyl group and R^1 is as described above.

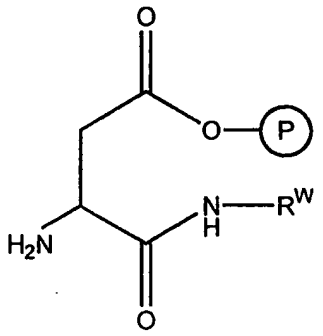
SCHEME 5



Again, in the Scheme 5, the amino function of the aminophenyl group on the left terminus of the substrate molecule is the "Y" function of an "Y-R^3" group, while portions of the CDI (carbonyldiimidazole) and the R^1-NH_2 reagents represent the "X" portion of an R^1-X reagent.

The modified aspartic acid that composes the right terminus of Formula 1 can be synthesized before adding such a modified residue to the remainder

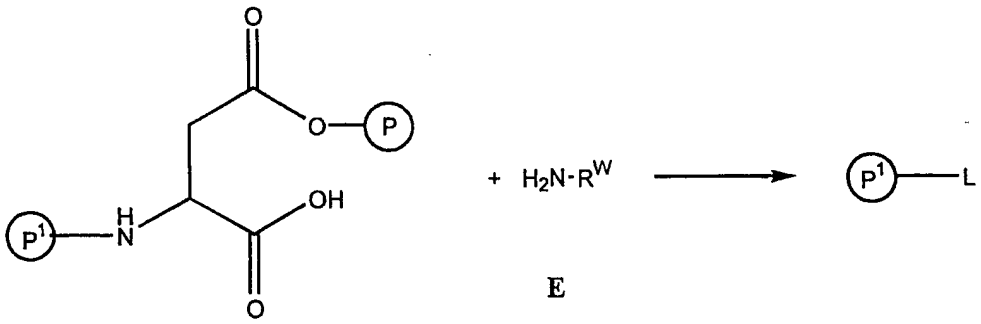
of the precursor molecule. In other words, a molecule of Formula L:



L

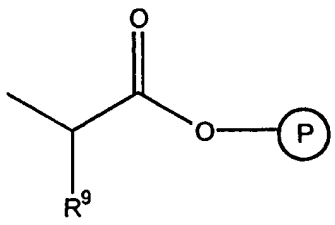
can first be synthesized by the following reaction Scheme 6:

SCHEME 6



D E

In the above reaction Scheme, P^1 -L represents **L** wherein the primary amino group is protected by protecting group P^1 . This protecting group is removed before **L** is coupled to the remainder of the precursor molecule. R^W in the above Scheme 6 can be R^6, as defined above for Formula 1, or a group of the Formula F:

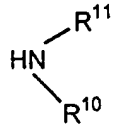


F

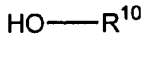
wherein the P is a carboxy protecting group and R^9 is as defined for Formula 1. In either case, any reactive subsituent on R^5 or R^9 can be selectively made temporarily unreactive, (i.e., "protected") and subsequent to said reactions, protected groups can be made reactive again (i.e., "deprotected"), by conditions and protecting groups known in the art for the purposes of the reactions in instant Schemes. The coupling reaction in Scheme 6 above is carried out under standard amino acid coupling conditions. Such conditions include the presence of a standard peptide coupling agent such as the combinations of dicyclohexylcarbodiimide(DCC) and 1-hydroxybenzotriazole(HOBt), N,N'-di(isopropyl)carbodiimide (DIC) and HOBt, and ethyl-3-(3-dimethylamino)-propylcarbodiimide (EDAC) and HOBt or HOAt (1-hydroxy-7-azabenzotriazole) as well as the BOP (benzotriazolyloxy-trio-(dimethylamino)phosphonium

hexafluorophosphate) reagent, pyBOP (benzotriazolyloxy-tris(N-pyrolidinyl)phosphoniumhexafluorophosphate), HBTU (O-benzotriazolyly-tetramethylisouronium-hexafluorophosphate), and EEDQ (1-ethyloxycarbonyl-2-ethyloxy-1,2-dihydroquinoline) reagents, and the like, as discussed in J. Jones, "Amino Acid and Peptide Synthesis," Steven G. Davis ed., Oxford University Press, Oxford, pp. 25-41 (1992); M. Bodanzky, "Principles of Peptide Synthesis," Hafner et al. ed., Springer-Verlag, Berlin Heidelberg, pp. 9-52 and pp. 202-251 (1984); M. Bodanzky, "Peptide Chemistry, A Practical Textbook," Springer-Verlag, Berlin Heidelberg, pp. 55-73 and pp. 129-180; and Stewart and Young, "Solid Phase Peptide Synthesis," Pierce Chemical Company, (1984), all of which are herein incorporated by reference.

When R^W is a group of Formula F, the synthesis of the right terminus of the molecule can be finished at any time before or during the reactions outlined below in Schemes 7 through 9, by removing the carboxy protecting group or removing it from the solid support and reacting it with groups of the Formulas G or H;



G

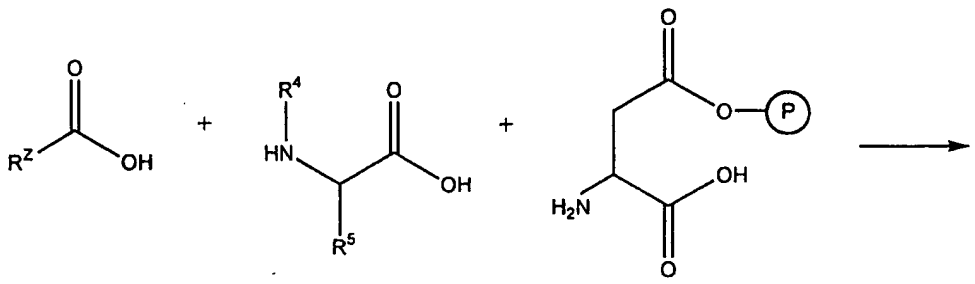


H

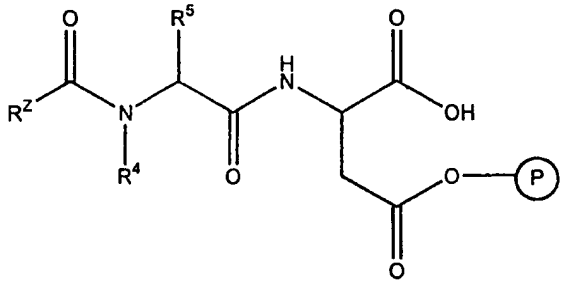
In the above Formulas G and H, R^{10} and R^{11} are as defined for Formula 1. These reactions would be carried out under standard coupling conditions for amide and ester forming reactions as described above and below.

Turning to the synthesis of the precursor molecule to Formula 1, Scheme 7 below sets forth a general synthetic strategy.

SCHEME 7



A I J



K

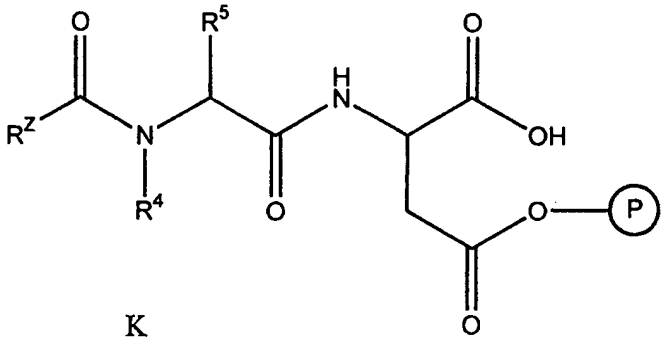
In the above Scheme 7, **A**, R^4, and R^5 are as discussed above. P is a carboxy protecting group. Reactive groups are appropriately protected and deprotected as needed. The reactions in the above

Scheme 7 can be carried out in solution phase. Thus, either **A** and **I** or **I** and **J** are coupled first, then the third subunit, either **J** or **A**, respectively, is added under standard peptide coupling conditions as discussed above for Scheme 6 to give the precursor molecule **K**.

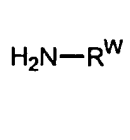
Similarly, the precursor molecule of **K** in the above Scheme 7 can be made by solid phase synthesis. Thus, **J** can be coupled to a solid support through the α-carboxy residue of the modified aspartic acid. First the residue of Formula **I** is coupled to **J** then **A** is coupled to **I** using the coupling conditions discussed above for Scheme 6. The bound precursor molecule is cleaved from the solid support to give that of **K**.

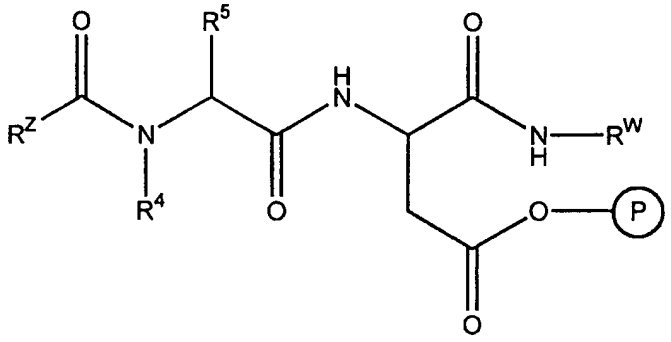
Scheme 8 below sets forth the strategy for completing the right terminus of a precursor molecule once the precursor backbone has been assembled using Scheme 7 above. Thus, the precursor molecular **K** is reacted with $H_2N\text{-}R^W$, wherein R^W is as described above for the synthesis of Formula **L**. The conditions used in Scheme 8 are standard peptide coupling conditions as discussed for the above Schemes.

SCHEME 8



K

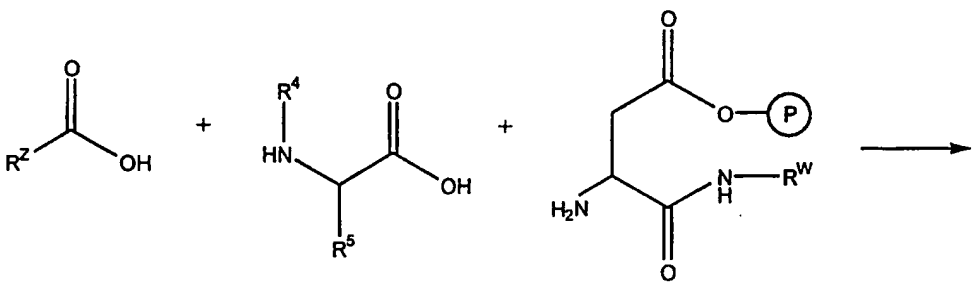




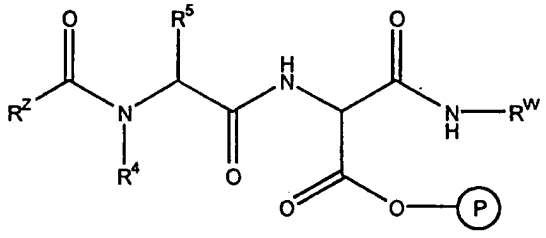
M

An alternate synthetic strategy for the precursor molecule is set forth below in Scheme 9.

SCHEME 9



A I L



M

In the above Scheme 9, **A** and **I** are those as discussed above for Scheme 7. Again, reactive groups are protected and deprotected as necessary. **L** is as discussed above for the synthesis of the right terminus. As with Scheme 7, the reaction set forth in

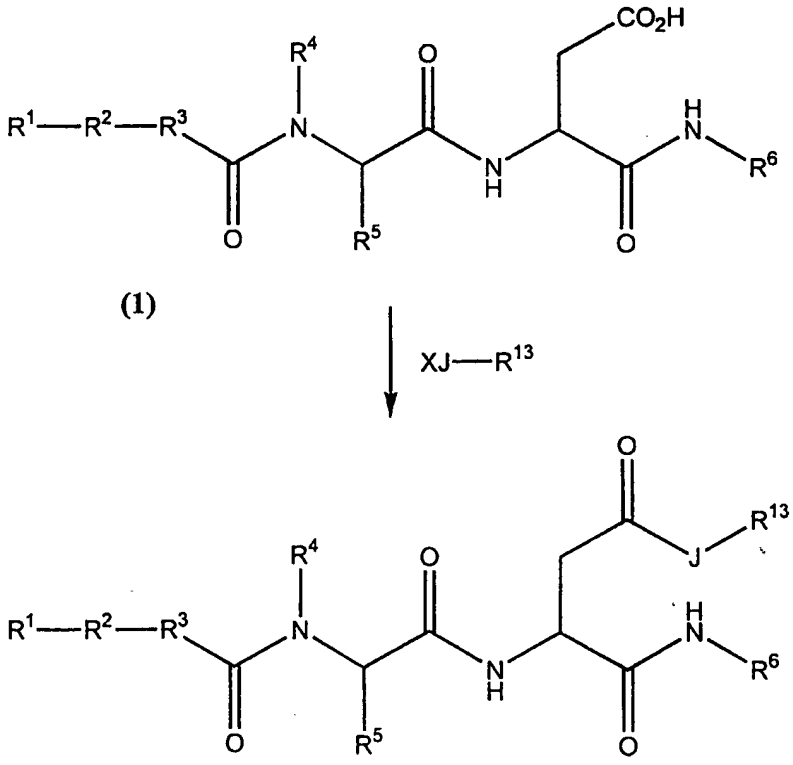
In the above scheme 10, the term "resin" is usally a Rink Amide MBHA resin or Wang resin. N-Fluorenymethoxcarbonyl (N-Fmoc) group is used for the protecting amino group of amino acid. Upon deprotecting of the Fmoc group with piperidine, the next N-Fmoc protected amino acid is coupled. That coupling is followed by further deprotecting, coupling, deprotecting, steps until a solid phase-linked compound of a desired sequence is prepared. For example, R, from Scheme 10, can be subsituted for J in Scheme 7 and Scheme 7 can be carried out in a similar fashion with R.

Finally, in Scheme 11 below, sets forth the general synthetic scheme for the pharmaceutically-acceptable derivatives of Formula 80. Thus, compounds of Formula 1 (with the appropriate substituents modified with protecting groups) are esterified with the compound of the formula XJ-R^{13}, wherein X is a hydrogen, chlorine, bromine or iodine atom, and J and R^{13} are as defined for Formula 80. The conditions used for this reaction are those for standard esterification procedures, such as the use of dicyclohexylcarbodiimide (DCC)/dimethylaminopyridine (DMAP) when X is hydrogen, or of sodium bicarbonate and sodium iodide when X is a halogen atom.

Moreover, the methods of synthesizing a pharmaceutically-acceptable derivative are known in the art. See, for example, Bundraard, "Design of Prodrugs," Elsevier Science Pub. Co., N.Y. (1985), "Prodrugs as Novel Drug Delivery Systems Symposium," 168th Annual Meeting, American Chemical Society, Atlantic City, N.J., Eds. T. Higuchi and V. Stella, ACS Symposium Serries 14, 1975, and Balant and Doelker, "Metabolic Considerations in Prodrug Design" in "Burger's Medicinal Chemistry and Drug Discovery,"

Vol. 1, Manfred E. Wolff, Ed., John Wiley & Sons, Inc., N.Y., 1994, pp949-982, which are herein incorporated by reference.

SCHEME 11



(1)

(29)

Regardless of the synthetic method used, a compound is typically recovered and purified prior to use.

Recovery and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, thin layer chromatography, preparative high pressure liquid chromatography, or a combination of these procedures. In addition, other equivalent separation or isolation procedures can also be used.

Various known methods can be used to characterize the structure of a compound of Formula 1 or pharmaceutically-acceptable derivative. Such methods include proton and ^{13}carbon nuclear magnetic resonance spectroscopy (NMR) and mass spectroscopy (MS). The ^{1}H-NMR spectra can be recorded, for example, on a GE QE-300, 300 MHz NMR spectrometer. MS can be analyzed on a PE-SCIEX API100 Electrospray mass spectrometer.

The VLA-4 inhibitory activity of a compound or a pharmaceutically-acceptable derivative can be analyzed by known methods and those described below. Known methods include, for example, assaying *in vitro* adhesion of radioactive cells that express VLA-4 to a substrate containing known VLA-4 receptors in the presence of the compound. See, for example, Elices *et al. Cell*, 60:577-584 (1990), which is incorporated herein by reference.

The anti-inflammatory activity of a compound of Formula (1) or a pharmaceutically-acceptable derivative of Formula (80) can be determined using a known animal model or assay for inflammation.

Known animal models include, for example, the measurement of dynamic compliance or lung resistance in asmatic animals, edema formation in delayed type hypersensitivity animal models, or allograft rejection in animals receiving organ transplants. See, for example, Molossi *et al. J. Clin. Invest.*, 95:2601-2610 (1995); Abraham *et al. J. Clin. Invest.*, 93:776-787 (1994); Elices *et al. Clin. Exp. Rheumatol.*, 11:S77-S80 (1993); Wahl *et al. J. Clin. Invest.* 94:655-662 (1994), which are incorporated herein by reference.

Also, the anti-inflammatory activity of a compound of Formula (1) or a pharmaceutically-acceptable derivative of Formula (80) can be measured in patients using known methods. For example, the number of painful joints or the amount of mobility in an arthritic patient can be measured.

This invention is further directed to a pharmaceutical composition comprising any of the compounds of Formula (1) and (80), and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle (hereinafter collectively referred to as "pharmaceutically-acceptable carriers"). Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin; buffer substances such as the various phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids; water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, and zinc salts; colloidal

silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyarylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat, and the like.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or by an implanted reservoir. Oral and parenteral administration are preferred. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable

oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carrier which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in capsule form useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These pharmaceutical compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible to topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active

components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-applied transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such pharmaceutical compositionss are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

As discussed above, the compound inhibits VLA-4 binding which prevents leukocyte movement into inflammed tissue and, thereby, treats or prevents inflammation. As such, the compound, pharmaceutically-acceptable derivative or pharmaceutical composition can treat or prevent inflammation in a wide range of conditions. For example, the invention can be used in the treatment or prevention of allergy, arthritis,

asthma, atherosclerosis, colitis, diabetes, inflammatory bowel disease, kidney inflammation, skin inflammatory diseases multiple sclerosis, restenosis, and transplantation are VLA-4 dependent inflammatory diseases and can be treated by a compound or pharmaceutically-acceptable derivative of the present invention.

Specific pathological inflammatory conditions include: rheumatoid arthritis (synovium), osteoarthritis (synovium), skin psoriasis, kidney transplant, asthmatic lung, and lymph node high endothelial venules (HEV) in humans, as well as in the gut of monkeys infected with SIV and those having inflammatory bowel disease, rabbits having asthmatic lungs and heart transplants, mouse brain in experimental autoimmune encephalomyelitis (EAE) and skin in delayed type hypersensitivity (DTH), and the joints of rats with induced arthritis.

The term "effective amount" refers to dosage levels of the order of from about 0.05 milligrams to about 140 milligrams per kilogram of body weight per day for use in the treatment of the above-indicated conditions (typically about 2.5 milligrams to about 7 grams per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 milligrams of the compound per kilogram of body weight per day (about 0.5 milligrams to about 3.5 grams per patient per day).

The amount of the compounds of Formula 1 or 80 that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from

0.5 milligrams to 5 grams of a compound of Formula 1 or 80 combined with an appropriate and convenient amount of a pharmaceutically-acceptable carrier which may vary from about 5 to about 95 percent of the total pharmaceutical composition. Dosage unit forms will generally contain between from about 1 milligram to about 500 milligrams of an active compound of Formula 1 or 80.

It will be understood, however, that the specific "effective amount" for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing prevention or therapy.

A compound's potency at inhibiting VLA-4 binding is used to screen compounds, but a compound's efficacy is the relevant parameter for clinical applications. Efficacy connotes the property of a drug to achieve a desired response. A compound having relatively low potency but more selectivity can be the preferred compound for a pharmaceutical composition.

The following examples are intended to more clearly illustrate aspects of the invention, but are not intended to limit the scope thereof.

Experimental Section

EXAMPLE 1

Starting Materials

The following protected amino acids: Boc-Phe-OH, Boc-Asp(OBzl)-OH, Boc-Leu-OH, Boc-N-Me-Leu, Boc-Ile, BocLys(Cbz)-OH, Pro methyl ester,. Fmoc-Pro, Fmoc-Phe, Fmoc-Asp(OBu^t), Fmoc-Leu, Fmoc-N-Me-Leucine, Fmoc-cyclohexylalanine, Fmoc-Gly, Fmoc-Ser(Bu^t), Fmoc-Met, Fomc-Nle, Fmoc-Tyr(Bu^t), Fmoc-Trp(Boc), Rink amide MBHA resin, MBHA resin, benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate(BOP), and di-t-butyl-carbonate (Boc_2O), N-(benzyloxycarbonyloxy)-succinimide were purchased from Novabiochem, La Jolla, CA. 4-Aminophenylacetic acid, morpholine, thiomorpholine, piperazine, 1-Bocpiperazine, 1-methylpiperazine, benzyl 2-bromoacetate, 2-bromo acetamide, o-tolyl isocyanate, benzyl isocyanate, 2-chlorophenyl isocyanate, 2-methoxyphenyl isocyanate, phenyl isocyanate, n-butyl isocyanate, cyclohexyl isocyanate, 4-aminophenylacetic acid, phenylacetic acid, allylbromide, 2-aminopyridine, 2-amino-3-methylpyridine, 4-dimethylaminopyridine (DMAP), N,N'-diisopropyl carbodimide (DIC), 4N HCl in dioxane, benzyl chloroformate, diisopropylethylamine (DIEA), triethylamine, N,O-dimethyl-hydroxylamine, lithium aluminum hydride ($LiAlH_4$), (S)-α-amino-ε-caprolactam,
triisopropylsilane (TIS), trifluoroacetic acid (TFA), triphenylmethyl chloride, acetic anhydride, 10% palladium on carbon, 2-chloro-N,N-dimethylacetamide, 1-hydroxybenzotriazole(HOBt), m-chloroperoxybenzoic acid(mCPBA), homopiperidine, anisole, methylsulfide, dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane (DCM) and various alcohols were

purchased from Aldrich Chemical Co., Milwaukee, WI. Ethyl-3-(3-dimethylamino)-propylcarbodimide - HCl (EDC) was obtained from Bachem Co., Torrance, CA. 1-hydroxy-7-azabenzotriazole (HOAt) was purchased from Perseptive Biosystems. Fmoc-β-(2-thienyl) alanine, and (3S)-Fmoc-3-amino-1-carboxymethyl-caprolactame were purchased from Neosystem. Tetrakis(triphenylphosphine) palladium (0) was purchased from Lancaster.

In the instant Example, the three-letter-abbreviation nomenclature known in the art is used to describe specific amino acids. For example, "Asp," "Leu," and "Phe" are used to represent the amino acids aspartic acid, leucine, and phenylalanine, respectively.

Preparative TLC plates (silica gel 0.25mm or 0.5mm x 20cm x 20cm) were purchased from Aldrich or VWR.

Analytical HPLC was conducted on either a Beckman System Gold Gilson System. The Beckman System Gold contains a model 507e autosampler, model no. 125 solvent module and model PDA 168 detector. The Gilson system contains a model 234 sampling injector, a model 119 UV/VIS detector, two model 306 pumps, a model 806 manometric module and 811C dynamic mixer. On both systems a Vydac Protein and Peptide C18 column (0.46 x 25 cm) was used. Flow rate: 1 ml/min, detected at 214 nm.

Preparative HPLC was conducted on Waters HPLC system comprising a with Water's 600E controller, and UV detector 441, and a Gilson's auto sampler 231 and fraction collector FC203B. A Vydac protein and peptide C18 semi-prep column (2.2 x 25 cm)

was used at a flow rate of 15 ml/min, detected at 215 nm.

The HPLC solvents were as follows: solvent A: water with 0.1% trifluoroacetic acid (TFA); solvent B: acetonitrile with 0.1% trifluoroacetic acid (TFA). Linear gradient conditions were usually used, as indicated in Table 1. For example, the gradient condition 5-70%B/35 min means that the concentration of HPLC solvent B increases from 5% to 70% over 35 min. The water used in the HPLC solvents is Milli Q water; acetonitrile was purchased from VWR, HPLC grade EM Science; and TFA (HPLC grade) was purchased from Pierce.

The ^{1}H-NMR spectra were recorded at 300 MHz on a GE QE-300 NMR spectrometer. The Mass spectrometry experimens were performed on an API 100 Perkin Elmer Sciex mass spectrometer. The electrospray technic was used in both positive mode, and negtive mode, usually yielding both MH^{+} and MH^{-}.

SOLUTION PHASE SYNTHESIS OF VLA-4 ANTAGONISTS

Synthesis of the compound of Formula (14)

4-(N'-(2-methylphenyl)urea)phenylacetyl-Leu-Asp-Phe-Morpholinamide

Preparations A through G set forth below in detail the preparation of the title compound.

Preparation A

Boc-Phe-Morpholinamide

A 250 ml flask was charged with Boc-Phe-OH (10 g, 38 mmol), morpholine (3.3 g, 38 mmol) and 1-hydroxybenzotriazole (HOBt) (5.1 g, 38 mmol) in 100 ml dry dimethylformamide (DMF). To this solution was added ethyl-3-(3-dimethylamino)-propylcarbodimide hydrochloride salt (EDC) (8.8 g, 46 mmol) at zero degree. The reaction mixture was slowly warmed to room temperature. The mixture was stirred for 8 hours at room temperature. DMF was removed by vacuum evaporator. To the residue were added ethyl acetate, and two layers were separated. The aqueous layer was extracted with ethyl acetate (70 ml x 2) the combined extracts were washed with 1N hydrochloric acid, water, saturated $NaHCO_3$, water and brine sequentially, dried over $MgSO_4$, filtered and concentrated to give a colorless liquid 12.8 g that was characterized by ^{1}H-NMR as Boc-Phe-Morpholinamide.

Preparation B

Phe-Morpholinamide Hydrochloride Salt

Boc-Phe-Morpholinamide (12.8 g, 38 mmol) was placed in a 250 ml flask, 4N HCl in dioxane (30 ml) was added. The mixture was stirred for 6 hours at which time thin layer chromatography (silica gel; $CHCl_3$: MeOH: acetic acid, 90 : 8 : 2) indicated that the reaction was completed. Dioxane and excess HCl were removed. A white solid, 10.3 g, identified by ^{1}H-NMR as Phe-Morpholinamide hydrochloride salt, was obtained.

Preparation C

Leu-Asp(OBzl)-Phe-Morpholinamide Hydrochloride Salt

Boc-Asp(OBzl)-OH and Boc-Leu-OH were sequentially added to Phe-Morpholinamide hydrochloride salt using the coulpling and deprotection procedures, described above. The white solid, thus obtained, was characterized by ^{1}H-NMR as the title product in total 95% yield.

Preparation D

4-(N-(benzyloxycarbonyl)Amino)-Phenyl Acetic Acid

To a suspension of 4-aminophenyl acetic acid (9.0 g, 60 mmol) and N-(benzyloxycarbonyloxy)-succinimide (15.0 g, 60 mmol) in 80 mL of methylene chloride was added 20 mL of triethylamine at which time a homogenous solution occurred. The resulting dark brown solution was then stirred at room temperature for 3 hours. The methylene chloride was removed by evaporation under vacuum and the resulting residue was dissolved in approximately 40 mL of water. The aqueous solution was then acidified by the addition of 5% HCl to pH3, at which time a brown solid precipitated out of solution. The solid was collected on a Buchner funnel and washed sequentially with 5% HCl, water and diethyl ether to give 14.2 g (84%) of the title product as a brown solid. ^{1}H-NMR (d^6-DMSO); 9.65-9.84 (s, 1H), 7.31-7.52 (m, 7H), 7.05-7.19 (d, 2H), 5.14 (s, 2H), 3.45 (s, 2H).

Preparation E

4-(N-(benzyloxycarbonyl)Amino)-Phenylacetyl-Leu-Asp(OBzl)-Phe-Morpholinamide

To a solution of 4-(N-(benzyloxycarbonyl)amino)-phenylacetic acid (942 mg, 3.3 mmol) and 1-hydroxybenzotriazole (445 mg, 3.3 mmol) in 20 mL of dry dimethylformamide at 0^0C was added EDC (759 mg, 3.9 mmol) and the remaining suspension was stirred at 0 C for 30 min. To this was then added the Leu-Asp(OBzl)-Phe- Morpholinamide hydrochloride salt (2.0 g, 3.3 mmol) followed immediately by addition of diisopropylethylamine to pH 6 (approximately 512 mg). The solution was then slowly warmed to room temperature where stirring continued overnight. The DMF was removed by evaporation, ethyl acetate and water were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (50 mL x 2), combined extracts were washed with 1N HCl, saturated $NaHCO_3$, water and brine. After drying with $MgSO_4$, the solution was filtered and concentrated to give 2.62 g (95%) of the coupled product as a pale yellow solid which was taken to the next step with no further purification. ^{1}H-NMR ($CDCl_3$); 7.15-7.42 (m, 21H), 6.69-6.67 (brs, 1H), 5.75-5.85 (d, 1H), 5.22 (s, 2H), 5.13 (d, 2H), 5.01 (m, 1H), 4.75 (m, 1H), 4.40 (m, 1H), 3.54 (s, 2H), 2.82-3.48 (m, 12H), 1.38-1.65 (m, 4H), 1.23-1.32 (t, 2H), 0.82-0.96 (d, 6H).

Preparation F

4-Aminophenacetyl-Leu-Asp-Phe-Morpholinamide

To a solution of 4-(N-(benzyloxycarbonyl)amino)-phenylacetyl-Leu-Asp(OBzl)-Phe-morpholinamide (2.6 g, 3.1 mmol) in 20 mL of methanol was added 200 mg of Pd/C and the resulting suspension was hydrogenated at 40 psi for overnight. The suspension was then filtered through filter paper to remove the charcoal and the methanol was removed by evaporation to give 1.75 g (94%) of the title product as a yellow solid which was taken to the next step with no further purification. ^{1}H-NMR (d^6-DMSO) 7.75-8.30 (m, 3H), 7.15-7.42 (m, 6H), 6.89-7.05 (d, 1H), 6.74-6.83 (m, 1H), 5.05-5.16 (m, 1H), 4.85-4.92 (m, 1H), 4.55-4.63 (m, 1H), 3.52 (s, 1H), 2.58-3.46 (m, 5H), 1.41-1.58 (m, 2H), 0.9 (m, 6H).

Preparation G

4-(N'-(2-methylphenyl)urea)phenylacetyl-Leu-Asp-Phe-Morpholinamide

To a solution of 4-Aminophenylacetyl-Leu-Asp-Phe-Morpholinamide (1.0 g, 1.6 mmol) in 15 mL of methylene chloride at rt was added o-tolyl isocyanate (327 mg, 2.4 mmol) followed by 1 drop of triethylamine. The resulting solution solidified to a gel after stirring for approximately 1 h. The gel was collected on a Buchner funnel and washed with copious amounts of methylene chloride to give 450 mg (36%) of slightly impure product. Further purification was achieved by preparative HPLC to give the pure urea as a white solid. ^{1}H-NMR (d^6-DMSO) 12.15-12.25 (br s, 1H), 9.00 (s, 1H), 8.16-8.30 (m, 2H), 7.75-8.02 (m, 3H), 7.12-7.41 9m,10H), 6.86-6.95 (t, 1H), 4.80-4.91 (m, 1H),

4.44-4.54 (m, 1H), 4.22-4.34 (m,1H), 2.36-3.41 (m, 15H), 2.22 (s, 3H), 1.35-1.68 (m, 3H), 0.72-0.89 (m, 6H). m/s (MH^+) 729.

This compound could also be made by an alternative way as described below for the compound of Formula (17).

Synthesis of the compound of Formula (17)

Preparation A

4-(N-(t-butyloxycarbonyl)Amino)-Phenylacetyl-Leu-Asp(OBzl)-Phe-Morpholinamide

4-(N-(t-Butyloxycarbonyl)amino)-phenyl acetic acid (0.927g, 3.71 mmol) coupled with HCl.Leu-Asp(OBzl)-Phe-Morpholinamide salt (1.75g, 3.71 mmol) by using the similar procedure as described in E. The title product (1.46 g) was obtained after purification by column chromatography (hexane:ethyl acetate= 1:4). ^{1}H-NMR ($CDCl_3$) δ 7.45-7.12 (m, 16H), 6.50 (s, 1H), 5.89 (d, 1H), 5.15 (dd, 2H), 5.05-4.94 (m, 1H), 4.80-4.70 (m, 1H), 4.45-4.35 (m, 1H), 3.56 (s, 2H), 3.55-2.68 (m, 2H), 1.68-1.45(m, 3H), 1.52 (s, 9H), 0.88(dd, 6H).

Preparation B

4-AminoPhenylacetyl-Leu-Asp(OBzl)-Phe-Morpholinamide

The compound from Step A was treated with 4N HCl in dioxane at room temperature as described above to give 4-amino-phenylacetyl-Leu-Asp(OBzl)-Phe-Morpholinamide.HCl salt as yellow solid.

Preparation C

4-(N'-(2-methoxyphenyl)urea)phenylacetyl-Leu-Asp-Phe-Morpholinamide

To a solution of 4-amino-phenylacetyl-Leu-Asp(OBzl)-Phe-Morpholinamide.HCl salt (72.2 mg, 0.1 mmol) in 10 ml of DCM at room temperature was added o-methoxylphenyl isocyanate (22.4 mg, 0.15 mmol) followed by 1 drop of triethylamine. After the reaction was completed, the solution was washed with 1N HCl and water. The DCM was removed, and the resultant residue was dissolved in 10 ml methanol, a catalytic amount of 10% Pd/C was added and the resulting suspension was hydrogenated overnight by using a hydrogen balloon. The suspension was then filtered and the methanol was removed by evaporation. The material was subjected to preparative HPLC purification (5-65%B over 45 min) to give the pure title product (10 mg). MS (m/z): 745 (MH^+).

The compounds of the Formulas (15), (56), (61) and (75) were prepared by the above methods.

Formulas (16), (21), (22), (25), (32), (57), (67) and (68) were synthesized by a similar method, i.e. the synthesis started from the right side to left side of molecule by incorporating each desired residue.

Regarding the compounds containing pyridyl or methylpyridyl urea moiety, the synthesis is slightly different. 4-(N'-(2-pyridyl)urea)phenyl acetic acid or 4-(N'-(2-(6-methylpyridyl))urea)phenyl acetic acid was prepared in advance. A representative procedure to prepare these two fragments is as follows (e.g. preparation of 4-(N'-(2-pyridyl)urea)phenyl acetic acid):

To a solution of 4-amino phenylacetic acid (1.5 g, 9.9 mmol) in methanol was added 4N HCl in dioxane (1 ml) and stirred overnight. The reaction was evaporated to give methyl 4-aminophenylacetate hydrochloride (1.7g). This compound (500 mg, 2.48 mmol) was mixed with DIEA (1.4 ml, 7.6 mmol) in DCM (20 ml) and cooled at 0^0C for 10 min. Phosgene (2.4 ml, 20% in toluene, 4.8 mmol) was added dropwise and the reaction mixture was stirred first for 30 min at 0^0C and then 3 hours at room temperature. The reaction mixture was concentrated by evaporation. To the residue was added DCM followed by DIEA (0.46 ml, 2.5 mmol) and 2-aminopyridine (260 mg, 2.77 mmol). The reaction mixture was stirred overnight. Removal of the solvent and column chromatography of the residue gave methyl 4-(N'-(2-pyridyl)urea)phenyl acetate (500 mg). This methyl ester (500 mg, 1.75 mmol) underwent hydrolysis by reflux with sodium hydroxide (280 mg, 7 mmol) in water (20 ml) and methanol (10 ml) until a clear solution was formed. The methanol was evaporated and the remaining solution was acidified with acetic acid. The white precipitant was filtered and washed with ethanol (5 ml x 2) to give the title product 4-(N'-(2-pyridyl)urea)phenyl acetic acid (290 mg). ^{1}H-NMR (DMSO-d_6): δ 10.5 (s, 1H), 9.3 (s, 1H), 8.2 (d, 1H), 7.7 (t, 1H), 7.4 (m, 3H), 7.1 (d, 2H), 6.9 (t, 1H), 3.5 (s, 2H).

4-(N'-(2-(6-methylpyridyl))urea)phenyl acetic acid obtained by this method was coupled to HCl.Leu-Asp(OBzl)-Phe-Morpholine followed by hydrogenolysis to give Formula (66).

4-(N'-(2-pyridyl)urea)phenyl acetic acid or 4-(N'-(2-(6-methylpyridyl))urea)phenyl acetic acid coupled with HCl-N-Me-Leu-Asp(OBzl)-Phe-(4-methyl)piperazine, which was prepared by the method

described in the synthesis of Formula (54), followed by hydrogenolysis gave Formulas (41) and (42) respectively.

Synthesis of the compound of Formula (54)

Preparation A

BocPhe-(N-methyl)piperazine

In a 250 round bottom flask, Boc-Phe (8.3 g, 31.29 mmol) and 1-methylpiperazine (3.1 g, 31.29 mmol) were dissolved in 100 ml DMF, cooled to -30°C with a bath (acetonitrile + dry ice). HOAt (or HOBt)(4.3 gram 31.29 mmol) and EDC (5.9 g, 31.29 mmol) were added and the reaction mixture was allowed to warm up to room temperature and then stirred overnight. The DMF solvent was removed under reduced pressure. EtOAc was added to the residue, and the resultant solution was washed with saturated sodium bicarbonate aqueous solution and brine. The solutoin was dried over magnesium sulfate. The product (10.8 g, 31.1 mmol) was obtained after filtration and evaporation.

Preparation B

Boc-N-Me-Leu-Asp(OBzl)-Phe-(N-methyl)piperazine

Boc-Phe-(N-methyl)piperazine (10.8 g, 31.1 mmol) was stirred with 4N Hcl (150ml) in dioxane for 2 hours. The starting material was completely consumed. The excess HCl and the solvent were then evaporated. Hcl-Phe-(N-methyl)piperazine (8.8 g, 31.0 mmol) was thus obtained. This product was coupled with Boc-Asp(OBzl) (10.1 g, 31.2 mmol) as procedure A (0°C instead of -30°C) to give 16.5 g Boc-Asp(OBzl)-Phe-(N-methyl) piperazine. By using the same

method, Boc-Asp(OBzl)-Phe-(N-methyl)piperizine was treated with 4N HCl in dioxane then further coupled with Boc-N-Me-Leu to give Boc-N-Me-Leu-Asp(OBzl)-Phe-(N-methyl)piperazine.

Preparation C

4-(N'-(o-tolyl)urea)-phenylacetyl-N-Me-Leu-Asp(OBzl)-Phe-(N-methyl)piperazine

1. Synthesis of 4-(N'-(o-tolyl)urea)-phenyl acetic acid

4-aminophenylacetic acid (15.0 g, 99.3 mmol) was placed in a 1000 ml round bottom flask. 500 ml ethyl acetate was added. To the stirring mixture was added 12.3 ml o-tolyl isocynate (12.3 ml, 99.3 mmol), the reaction mixture was stirred for 1 hour at room temperature and then heated to reflux for another hour. The reaction mixture was then cooled to room temperature and filtered to give the solid product. The solid was recrystallized in methanol twice to provide 18.0 g of the title product. ^{1}H-NMR (DMSO-d_6): δ 9.0 (s, 1H), 7.9 (s, 1H), 7.8 (d, 1H), 7.3 (d, 2H), 7.2 (m, 4H), 6.9 (m, 1H), 3.5 (s, 2H), 2.2 (s,3H).

2. Synthesis of 4-(N'-(o-tolyl)urea)-phenylacetyl-N-Me-Leu-Asp(OBzl)-Phe-(N-methyl)piperazine

Boc-N-Me-Leu-Asp(OBzl)-Phe-(N-methyl)piperizine (5.8 g, 8.9 mmol) was treated with 4N HCl in dioxane, further coupled with 4-(N'-(o-tolyl)urea)-phenyl acetic acid (2.53 g, 8.9 mmol). The 4-(N'-(o-toluyl)urea)-phenylacetyl-N-Me-Leu-Asp(OBzl)-Phe-(N-methyl)piperazine was obtained. The reaction protocol was the same as described above. This benzyl

ester of Formula (54) was purified by silica gel flash column chromatography, using EtOAc and methanol (from 90:1 to 90:10) as the eluent to give 6.8 g of the title product was obtained.

Preparation D

Synthesis of Formula (54) from its benzyl ester

The above benzyl ester (1.66 g, 1.96 mmol) was dissolved in 200 ml methanol. The solution was flashed with argon. A catalytic amount of 10% palladium on activated carbon was added. The mixture was flashed with hydrogen. The reaction was carried out under a H_2 atmosphere by using a hydrogen balloon for seven hours. TLC showed the starting material was completely consumed. The solid residue was filtered off by a celite-packed funnel. The pure compound Formula (54) (1.28 g) was obtained after concentration. ^{1}H-NMR(DMSO-d_6): δ 8.95 (s,1H), 6.85-8.40 (m, 16H), 5.45-5.65 (m, 2H), 5.00-5.15 (m, 2H), 4.75-4.90 (m, 2H), 3.00-3.80 (m, 7H), 2.00-2.90 (m, 10H), 0.60-1.90 (m, 9H). MS (m/z): 756(MH^+), 754 (MH^-).

General procedure for synthesis of the compound of Formulas (18), (30), (31), (34), (45), (49), (53), (58), (59) and (60)

Preparation A

Boc-Leu-Asp(OBzl)Phe-O-Allyl

To a mixture of Boc-Phe (3.0 g, 11.3 mmol) and Na_2CO_3 (1.8 g, 16.95 mmol) in 100 ml DMF was added allyl bromide (3.9 ml, 45.23 mmol). The reaction

mixture was stirred overnight at room temperature. The solid was filtered off and DMF was evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with 1N HCl, saturated aqueous sodium bicarbonate and brine, then dried over magnesium sulfate. The solution was concentrated to give 3.2 g Boc-Phe-OAllyl. The title product Boc-Leu-Asp(OBzl)-Phe-OAllyl was obtained by treating Boc-Phe-OAllyl with 4N HCl followed by coupling with Boc-Asp(OBzl) to form Boc-Asp(OBzl)-Phe-OAllyl. The Boc group was removed with 4N HCl in dioxane followed by coupling with Boc-Leu to form Boc-Leu-Asp(OBzl)-Phe-O-Allyl. The reaction protocol was the same as described above.

Preparation B

4-(N'-(o-tolyl)urea)-phenylacetyl-Leu-Asp(OBzl)-Phe-O-Allyl

The Boc was removed from Boc-Leu-Asp(OBzl)Phe-O-Allyl (624 mg, 1.0 mmol). The product was dissolved in DMF (1.5 mL) and the pH was adjusted to pH 9 by addition of DIEA (0.174 ml, 1.0 mmol). EDC (192 mg, 1.0 mmol) was added to a solution of 4-(N'-(o-tolyl)urea)-phenyl acetic acid (256 mg, 0.9 mmol) and HOBt (135 mg, 1.0 mmol) in DMF (1.5 ml) at 0°C, and the reaction was allowed to proceed for 30 min at 0°C. To this mixture was added the solution of HCl-H-Leu-Asp(OBzl)-Phe-O-Allyl and DIEA prepared as described above. The reaction mixture was allowed to warm to room temperature and stirred overnight. After dilution with ethyl acetate (50 ml) the solution was washed with saturated sodium bicarbonate, 1N hydrochloric acid and water. A gel-like precipitate formed during the washing process, which was isolated by filtration and washed with ethyl acetate. After drying in vacuo the title product (672 mg, 0.85 mmol, 95 %) was obtained as

a white powder. ^{1}H-NMR (DMSO-d_6) δ 9.36 (s, 1H), 8.22 (d, J = 7.7 Hz, 1H), 8.10-8.15 (m, 3H), 7.74 (d, J = 8.1 Hz, 1H), 7.00-7.29 (m, 16 H), 6.79-6.84 (m, 1H), 5.62-5.75 (m, 1H), 5.13 (dd, J = 17.2 Hz, 1.5 Hz, 1H), 5.06 (dd, J = 10.3, 1.1 Hz, 1H), 4.99 (d, J = 12.8 Hz, 1H), 4.94 (d, J = 12.8 Hz, 1H), 4.52-4.59 (m, 1H), 4.31-4.43 (m, 3H), 4.13-4.20 (m, 1H), 3.22-3.37 (m, overlaps with H_2O), 2.84-2.90 (m, 2H), 2.69 (dd, J = 16.5, 5.1 Hz, 1H), 2.53 (dd, J = 16.5, 8.8 Hz, 1H), 2.16 (s, 3H), 1.25-1.55 (m, 3H), 0.75 (d, 3H), 0.70 (d, 6.2 Hz, 3H).

Preparation C

4-(N'-(o-tolyl)urea)-phenylacetyl-Leu-Asp(OBzl)-Phe-OH

The above allyl ester (474 mg, 0.6 mmol) was dissolved in DMF (3 ml) under an atmosphere of argon and the solution was cooled to 0°C. Morpholine (0.52 ml, 6 mmol) was added followed by tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol) and the mixture was stirred for 30 min at 0°C. After dilution with ethyl acetate (400 ml) the mixture was washed with 1N hydrochloric acid and brine. After removal of the solvent under reduce pressure the title product (470 mg) was obtained as a white powder which was used for the following steps without further purification. ^{1}H-NMR (DMSO-d_6) δ 8.95 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.1 Hz), 7.89 (s, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.21-7.27 (m, 7 H), 7.00-7.20 (m, 9 H), 6.80-6.86 (m, 1H), 4.95 (s, 2H), 4.50-4.58 (m, 1H), 4.15-4.23 (m, 1H), 3.17-3.36 (m, overlaps with water), 2.45-2.95 (m, 4H), 2.13 (s, 3H), 1.27-1.53 (m, 3H), 0.74 (d, J = 6.6 Hz, 3H), 0.69 (d, J = 6.2 Hz, 3H).

Preparation D

General Procedure: Coupling of 4-(N'-(o-tolyl)urea)-phenylacetyl-Leu-Asp(OBzl)-Phe-OH to Various Amines

4-(N'-(o-tolyl)urea)-phenylacetyl-(N-methyl)Leu-Asp(OBzl)-Phe-OH(79 mg, 0.1 mmol), HOAt (14 mg, 0.1 mmol), and the amine (0.11 mmol) were dissolved in DMF (0.5 ml), and the solution was cooled to -48°C. If an amine.HCl salt was to be coupled, DIEA (0.02 ml, 0.11 mmol) was included in the reaction mixture. EDC (0.019 ml, 0.1 mmol) was added and the reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with 1N hydrochloric acid, saturated sodium bicarbonate, and brine. After drying with magnesium sulfate and filtering, the solvent was removed under reduced pressure. The products obtained in this way were used for the following steps without further purification.

Preparation E

General Procedure: Hydrogenolysis of Benzyl Esters

The benzyl ester was dissolved in DMF and the solution was saturated with argon. After addition of palladium on carbon (10% w/w) the mixture was stirred under an atmosphere of hydrogen for 4 to 15 h. The catalyst is removed by filtration over a bed of celite and the solvent is removed under reduced pressure. The final product was purified by preparative HPLC.

If the N-Me-leucine was incorporated instead of leucine in the molecules, the synthetic methods were the same except Boc-N-Me-Leu was employed.

In order to prepare the compounds of Formulas (49) and (60), 1-(benzyl acetate)-piperazine was used to couple to the left side of molecule followed by hydrogenolysis to remove two benzyl esters. 1-Boc-piperazine was used to couple to the left side of molecule followed by treatment of 4N HCl and hydrogenolysis to produce Formula (53).

Regarding the synthesis of Formula (34), the following procedure was used:

4-(N'-(o-tolyl)urea)-phenylacetyl-Leu-Asp(OBzl)-Phe-OH was coupled to thiomorpholine by the method described in general procedure D. The product (20mg, 0.024 mmol) was dissolved in DMF (5 ml) and the solution was cooled to 0°C. mCPBA (80 mg, 50-60% pure) was added, and the mixture was allowed to warm to room temperature and stirred overnight. The mixture was concentrated under reduced pressure to 1 ml and the title product was precipitated by addition of ether (20 ml). After centrifugation the supernatant was separated from the pellet by decantation and the pellet was washed twice with ether. After drying in vacuo the product (20 mg) was dissolved in DMF (1 ml) and the benzyl ester was cleaved according to general procedure E. Formula (34) (1.1 mg) was obtained after purification by HPLC as a white powder.

Synthesis of (S)-3-amino homopiperidine containing molecules: Formulas (39), (47), (76), (77) and (79)

Preparation A

Boc-Asp(OBzl)-O-Allyl

Boc-Asp(OBzl)-OH (3.23 g, 10 mmol) was dissolved in DMF. Sodium bicarbonate (1.68 g, 20 mmol)

was added followed by allylbromide and the mixture was stirred overnight at room temperature. After dilution with ethyl acetate (100 ml) the mixture was washed with water, saturated sodium bicarbonate, and 1 N hydrochloric acid and dried with magnesium sulfate. After filtering and removal of the solvent under reduced pressure the title product was obtained as a colorless oil (3.59 g, 9.88 mmol, 99%). ^{1}H-NMR ($CDCl_3$) 7.40-7.30 (m, 5H), 5.78-5.91 (m, 1H), 5.49 (d, J = 8.1 Hz, 1H), 5.29 (dd, J = 1.1 Hz, 17.2 Hz, 1H), 5.22 (dd, J = 1.1 Hz, 10.6 Hz,1H), 5.13 (s, 2H), 4.60 (d, J = 5.9 Hz, 2H), 4.59-4.64 (m, 1H), 3.07 (dd, J = 4.4 Hz, 16.9 Hz, 1H), 2.88 (dd, 4.8 Hz, 16.9 Hz, 1H), 1.45 (s, 9H).

Preparation B

Boc-Leu-Asp(OBzl)-O-Allyl

Boc-Asp(OBzl)-OAllyl (3.59 mg, 9.88 mmol) was reacted with 4 N HCl in dioxane for 1 h at room temperature. After removal of the solvent under reduced pressure, the product was dried in vacuo. This material was dissolved in DMF (20 ml) and the pH was adjusted to pH 9 by addition of DIEA (1.74 ml, 10 mmol). HOBt (1.89 g, 14 mmol) was added followed by Boc-Leu-OH·H_2O (3.24 g, 14 mmol), and the mixture was cooled to 0°C. EDC (2.68 g, 14 mmol) was added and the reaction was allowed to warm to room temperature and stirred overnight. After removal of the solvent under reduced pressure the residue was taken up in ethyl acetate (100 ml) and washed with 1N hydrochloric acid, saturated sodium bicarbonate, and brine. After drying with magnesium sulfate and filtering the solvent was removed under reduced pressure. The title product (5.54 g) was obtained as a yellow oil which was used for the following step without further purification.

Preparation C

4-(N'-(o-tolyl)urea)-phenylacetyl-Leu-Asp(OBzl)-O-Allyl

The Boc group was removed from Boc-Leu-Asp(OBzl)-O-Allyl (5.54 mg,) as described above. The title product (4.74 g) as obtained as a yellow oil. The hydrochloride salt(2.77 g) was dissolved in DMF (5 ml) and the pH was adjusted to pH 9 by addition of DIEA (0.87 ml, 5 mmol). EDC (633 mg, 3.3 mmol) was added to a solution of 4-(N'-(o-tolyl)urea)-phenyl acetic acid (853 mg, 3.0 mmol) and HOBt (405 mg, 3.0 mmol) in DMF (5 ml) at 0°C and the reaction was allowed to proceed for 30 min at 0°C. To this mixture was added the solution of HCl.H-LeuAsp(OBzl)-O-Allyl and DIEA prepared as described above. The reaction mixture was allowed to warm to room temperature and stirred overnight. After dilution with ethyl acetate (300 ml) the solution was washed with 1N hydrochloric acid, saturated sodium bicarbonate, and brine. After removal of the solvent under reduced pressure the title product (1.99 g, 3.1 mmol) was obtained as a yellow solid which was used for the following step without further purification. ^{1}H-NMR (DMSO-d_6) δ 8.93 (s, 1H), 8.46 (d, J = 7.7 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.22-7.29 (m, 7H), 7.01-7.08 (m, 4H), 6.83 (app t, J = 7.3 Hz, 1H), 5.66-5.79 (m, 1H), 5.19 (dd, J = 1.5 Hz, 17.2 Hz, 1H), 5.08 (dd, J = 1.5 Hz, 10.3 Hz, 1H), 4.99 (s, 2H), 4.57-4.64 (m, 1H), 4.42 (d, J = 5.1 Hz, 1H), 4.20-4.28 (m, 1H), 2.80 (dd, J = 6.2 Hz, 16.5 Hz, 1H), 2.67 (dd, J = 7.0, 16.5 Hz, 1H), 2.14 (s, 3H), 1.30-1.53 (m, 3H), 0.76 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.2 Hz, 3H).

Preparation D

4-(N'-(o-tolyl)urea)-phenylacetyl-Leu-Asp(OBzl)-OH

4-(N'-(o-tolyl)urea)-phenylacetyl-Leu-Asp(OBzl)-OAllyl (1.48 g, 2.3 mmol) was dissolved in DMF (15 ml) under an atmosphere of argon. Morpholine (2.5 ml, 30 mmol) was added followed by tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.029 mmol). After stirring at room temperature for 30 min the mixture was poured into 1N hydrochloric acid (200 ml). A precipitate formed which was isolated by filtration and washed with water. After drying in vacuo the title product (1.55 g, 2.57 mmol) was obtained as a pale yellow powder which was used for the following steps without further purification. ^{1}H-NMR (DMSO-d_6) δ 12.8 (s, 1H), 8.90 (s, 1H), 8.26 (d, J = 7.7 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.81 (s, 1H), 7.74 (d, 7.7 Hz, 1H), 7.22-7.30 (m, 7H), 7.01-7.08 (m, 4H), 6.81-6.86 (app t, J = 7.3 Hz, 1H), 4.99 (S, 2H), 4.47-4.54 (m, 1H), 4.19-4.27 (m, 1H), 2.58-2.79 (m, 2H), 2.14 (s, 3H), 1.30-1.60 (m, 3H), 0.69-0.77 (m, 6H).

4-(N'-(o-tolyl)urea)-phenylacetyl-N-Me-Leu-Asp(OBzl)-OH was prepared by the same method as described above, except that Boc-N-Me-Leu was used in place of Boc-Leu. ^{1}H-NMR (DMSO-d_6) 12.76 (br s, 1H), 8.88 (s, 1H), 8.07(d, J = 8.4 Hz, 1H), 7.79 (s, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.24-7.30 (m, 7H), 7.00-7.08 (m, 4H), 6.81-6.86 (m, 1H), 4.99-5.03 (m, 1H), 4.99 (s, 2H), 4.50-4.57 (m, 1H), 3.61 (d, J = 15.6 Hz, 1H), 3.48 (d, J = 15.0 Hz, 1H), 2.80 (dd, J = 5.49 Hz, 16.1 Hz, 1H), 2.60-2.68 (m, 1H), 2.66 (s, 3H), 2.14 (s, 3H), 1.10-1.65 (m, 3H), 0.72-0.76 (m, 6H).

Preparation E

(S)-Boc-Lys(Cbz)-NMe(OMe)

DIEA (4.35 ml, 35 mmol) was added to a solution of Boc-Lys(Cbz)-OH (9.51 g, 25 mmol) and the resulting mixture was cooled to 0°C. BOP (11.1 g, 25 mmol) was added in one portion and the mixture was stirred for 10 min at 0°C. N,O-Dimethyl-hydroxylamine hydrochloride (2.68 g, 27.5 mmol) was added followed by DIEA (4.79 ml, 27.5 mmol) and the mixture was stirred for 1 h at rt. After diluting with DCM (100 ml) the solution was washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and water and dried with magnesium sulfate. After filtering and removal of the solvent under reduced pressure the title product was obtained as a colorless oil (9.52 g, 22.5 mmol, 90%). ^{1}H-NMR ($CDCl_3$) 7.26-7.36 (m, 5H), 5.12 (d, J= 8.1 Hz, 1H), 5.09 (s, 2H), 4.83-4.92 (m, 1H), 4.60-4.71 (m, 1H), 3.76 (s, 3H), 3.20 (s, 3H), 3.12-3.26 (m, 2H), 1.30-1.85 (m, 6H), 1.42 (s, 1H).

Preparation F

Boc-Lys(Cbz)-CHO

Boc-Lys(Cbz)-NMe(OMe) (985 mg, 2.33 mmol) was dissolved in anhydrous THF (20 ml) under an argon atmosphere and the solution was cooled on an ice-bath. A solution of $LiAlH_4$ in diethyl ether (3ml, 1N) was added dropwise with a syringe and the mixture was stirred for 30 min at 0°C. After quenching with a solution of $KHSO_4$ (0.57g) in water (10 ml) the mixture was extracted three times with ethyl ether. The combined extracts were washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine and dried with magnesium sulfate. After filtering and removal of

the solvent under reduced pressure the title product was obtained as a colorless solid (796 mg, 2.18 mmol, 94%). ^{1}H-NMR ($CDCl_3$) δ 9.50 (s, 1H), 7.22-7.33 (m, 5H), 5.12 (br s, 1H), 5.04 (s, 2H), 4.79 (br s, 1H), 4.13-4.21 (m, 1H), 3.08-3.21 (m, 2H), 1.40-1.95 (m, 6H), 1.38 (s, 9H).

Preparation G

(S)-3-t-Butyloxycarbonylamino-homopiperidine

Boc-Lys(Cbz)-CHO (796 mg, 2.18 mmol) was dissolved in methanol (450 ml) and the solution was saturated with argon. After addition of palladium on carbon (10%, 80 mg) the mixture was stirred under an atmosphere of hydrogen for 3 days. The catalyst was removed by filtration over a bed of celite and the solvent was removed under reduced pressure. The title product (472 mg, 2.20 mmol, 100%) was obtained as a pale yellow oil which was used for the next step without further purification. ^{1}H-NMR ($CDCl_3$) 5.08 (br s, 1H), 3.69-3.81 (m, 1H), 2.72-2.96 (m, 4H), 1.50-178 (m, 7H), 1.44 (s, 9H).

Preparation H

N-Acetyl-(S)-3-t-Butyloxycarbonylamino-homopiperidine

Acetic anhydride (0.142 ml, 1.5 mmol) was added to a solution of (S)-3-t-butyloxycarbonylamino-homopiperidine (236 mg, 1.1 mmol) and DIEA (0.262 ml, 1.5 mmol) in dichloromethane (4 ml), and the resulting mixture was stirred for 2 h at rt. The solution was then washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine and dried with magnesium sulfate. After filtering and removal of the solvent under reduced pressure the product was purified by

flash chromatography (eluent: ethyl acetate). The title product was obtained as a colorless oil (189 mg, 0.74 mmol, 67%) which crystallized upon drying in vacuo. ^{1}H-NMR ($CDCl_3$) δ 5.87 (br s, 1H), 4.52-4.63 (m, 1H), 3.64-4.07 (m, 2H), 2.98-3.30 (m, 2H), 2.14 (s, 1H), 2.06 (s, 2H), 1.36-1.86 (m, 15H).

Preparation I

N-Aminocarbonylmethyl-(S)-3-t-Butyloxycarbonylamino-homopiperidine

2-Bromoacetamide (0.47 g, 3.4 mmol) was added to a solution of (S)-3-t-butyloxycarbonylamino-homopiperidine (0.73 g, 3.4 mmol) and DIEA (0.60 ml, 3.4 mmol) in dichloromethane (10 ml), and the resulting mixture was stirred overnight at room temperature. The solution was then washed with saturated sodium bicarbonate and water and dried with magnesium sulfate. After filtering and removal of the solvent under reduced pressure the product was purified by flash chromatography (eluent: chloroform: acetone 7:3). The title product was obtained as a colorless oil (483 mg, 1.78 mmol, 52%) which crystallized upon drying in vacuo. ^{1}H-NMR ($CDCl_3$) δ 6.95 (br s, 1H), 5.63 (br s, 1H), 4.69 (d, J= 5.1 Hz, 1H), 3.68-3.83 (m, 1H), 3.19 (s, 2H), 2.85-2.95 (m, 1H), 2.58-2.83 (m, 3H), 1.45-2.05 (m, 6H), 1.44 (s, 9H).

Preparation J

N-Benzyloxycarbonylmethyl-(S)-3-t-butyloxycarbonylamino-homopiperidine

Benzyl 2-bromoacetate (2.53 ml, 15.9 mmol) was added to a solution of (S)-3-

t-butyloxycarbonylamino-homopiperidine (3.43 g, 3.4 mmol) and DIEA (2.8 ml, 3.4 mmol) in dichloromethane (30 ml), and the resulting mixture was stirred for 48 h at room temperature. The solution was then washed with saturated sodium bicarbonate and water and dried with magnesium sulfate. After filtering and removal of the solvent under reduced pressure the product was purified by flash chromatography (eluent: ethyl acetate - hexanes 3:7). The title product was obtained as a colorless oil (2.71 g, 7.5 mmol, 47%) which crystallized upon drying in vacuo. ^{1}H-NMR ($CDCl_3$) δ 7.28-7.37 (m, 5H), 5.58 (d, J = 5.9 Hz, 1H), 5.18 (d, J = 12.5 Hz, 1H), 5.13 (d, J = 12.5 Hz, 1H), 3.66-3.78 (m ,1H), 3.46 (s, 1H), 3.03 (dd, J = 2.2 Hz, 14.3 Hz, 1H), 2.64-2.78 (m, 3H), 1.50-1.85 (m, 6H), 1.45 (s, 9H).

Preparation K

Synthesis of N-Carboxymethyl-(S)-3-t-butyloxycarbonylamino-homopiperidine

N-Benzyloxycarbonylmethyl-(S)-3-t-butyloxycarbonylamino-homopiperidine (2.71 g, 7.5 mmol) was dissolved in methanol and the solution was saturated with argon. After addition of palladium on carbon (10%, 300 mg) the mixture was stirred under an atmosphere of hydrogen for 4 h. The catalyst was removed by filtration over a bed of celite and the solvent was removed under reduced pressure. The title product (2.07 g, 7.60 mmol) was obtained as an amorphous foam which was used for the following step without further purification. ^{1}H-NMR ($CDCl_3$) δ 6.66 (d, J = 7.7 Hz, 1H), 3.33-3.48 (m, 1H), 3.25 (d, J = 17.2 Hz, 1H), 3.18 (d, J =17.2 Hz, 1H), 2.61-2.76 (m, 4H), 1.35-1.60 (m, 6H), 1.27 (s, 9H).

Preparation L

Synthesis of N-(Dimethylaminocarbonyl)-methyl-(S)-3-t-butyloxycarbonylamino-homopiperidine

N-Carboxymethyl-(S)-3-t-butyloxycarbonylamino-homopiperidine (72 mg, 0.26 mmol), HOBt (27 mg, 0.20 mmol), and dimethylamine hydrochloride (18 mg, 0.22 mmol) were dissolved in DMF (1 ml). DIEA (0.038 ml, 0.22 mmol) was added followed by EDC (38 mg, 0.22 mmol), and the reaction was stirred at room temperature for 2.5 h. The mixture was diluted with ethyl acetate (10 ml), washed with saturated sodium bicarbonate and brine, and dried with sodium sulfate. After filtering the product was purified by flash chromatography (dichloromethane: acetone 1:1). The title product N-(dimethylaminocarbonyl)-methyl-(S)-3-t-butyloxycarbonylamino-homopiperidine(23 mg, 0.077 mmol, 38%) was obtained as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 5.66 (d, 1H), 3.65-3.76 (m, 1H), 3.33-3.44 (m, 2H), 3.04 (s, 3H), 2.95 (s, 3H), 2.87-3.00 (m, 1H), 2.65-2.85 (m, 3H), 1.45-1.85 (m, 6 H), 1.45 (s, 9H). Boc was then removed by treatment of 4N HCl in dioxane. After removal of excess HCl and dioxane, N-(dimethylaminocarbonyl)-methyl-(S)-3-amino-homopiperidine-HCl salt was obtained.

N-aminocarbonylmethyl-(S)-3-amino-homopiperidine can also been prepared by the following method:

Preparation M

N-aminocarbonylmethyl-(S)-3-amino-homopiperidine

To the mixture of S-α-amino-ϵ-caprolactam (1.79 g, 14 mmol) and triphenylmethyl chloride (4.5 g, 16 mmol) in anhydrous THF (50 ml) and DMF (50 ml) was added triethylamine(3.5 mg, 35 mmol). The resultant mixture was stirred for 20 hours. The solvents were evaporated and water was added to the residue. The aqueous solution was extracted twice with ethyl acetate. The ethyl acetate concentrate was subjected to column chromatography (hexane/ethyl acetate: 7/3 to 5/5) to yield the product (S)-trityl- α-amino-ϵ-caprolactam 2.35 g.

(S)-trityl-α-amino-ϵ-caprolactam (1.41 g, 3.81 mmol) was dissolved in anhydrous THF (15 ml) 1N $LiAlH_4$ in ether (11 ml, 11 mmol) was added in a dropwise fashion. The mixture was refluxed for 4 hours. The reaction mixture was cooled on an ice bath, then a saturated Na_2SO_4 aqueous solution was added in a dropwise fasion until no more bubbles were generated. The white solid was filtered off and washed with ethyl acetate 3 times. The combined solution was evaporated to dryness. Ethyl acetate was added to the residue, the solution was dried over Na_2SO_4. After filtration and evaporation, (S)-trityl-3-amino-homopiperidine was obtained as a pale yellow oily material (1.1 g). This compound reacted with 2-bromoacetamide to form N-aminocarbonylmethyl-(S)-trityl-3-amino-homopiperidine, the latter of which was treated with 2N HCl in dioxane and DCM to form N-aminocarbonylmethyl-(S)-3-amino-homopiperidine.HCl salt.

Preparation N

Synthesis of the compound of Formula (76)

N-aminocarbonylmethyl-(S)-3-amino-homopiperidine.HCl salt (59 mg, 0.24 mmol) was dissolved in DMF (1 ml), and the pH of the solution was adjusted to pH 9 by addition of DIEA (0.084 ml, 0.48 mmol). To this solution was added 4-(N'-(o-tolyl)urea)-phenylacetyl-Leu-Asp(OBzl)-OH (120 mg, 0.2 mmol) followed by HOAt (27 mg, 0.20 mmol), and the solution was cooled to -48°C. EDC (46 mg, 0.24 mmol) was added and the reaction was allowed to warm to room temperature then stirred overnight. The reaction mixture was diluted with ethyl acetate (100 ml) and washed with 1N hydrochloric acid, saturated sodium bicarbonate, and brine. After drying with magnesium sulfate and filtering the solvent was removed under reduced pressure. The product was dissolved in DMF (1.5 ml) and the benzyl ester was removed by hydrogenolysis as described above. The product (135 mg) was subjected to preparative HPLC to yield Formula (76) as a white powder.

Formulas (39,) (47), (77) and (79) were prepared by the same procedure.

SOLID PHASE SYNTHESIS

A. Fmoc strategy

The Fmoc-Rink Amide MBHA resin was washed three times with DMF, then treated with 20% piperidine in DMF for 5 min. The solution was drained by filtration and the resin was again treated with 20% piperidine in DMF for 20 min. The solution was drained by filtration, and the resin was washed five times with DMF, once with

isopropanol and four times with DMF. The 3 equivalent of HOBt ester of Fmoc-D-proline in DMF (formed by reacting a solution of equimolar amount of F-moc-D-proline, HOBt and DIC in DMF) was added to the resin and allowed to react for 2 hours. The resin was washed five times with DMF, once with isopropanol, two times with DMF and two times with DCM. The coupling of amino acid to the resin was then checked by standard Kaiser's test.

The above cycle was iterated for each of the subsequent amino acids. For exmaple: Fmoc-Phe, Fmoc-Asp(OBu^t), Fmoc-Leu and 4-Fmoc-aminophenyl acetic acid were sequentially coupled. Thus 4-FmocNH-Phenylacetyl-Leu-Asp(OBu^t)-Phe-Pro(Rink amide MBHA resin) was assembled. After removal of the Fmoc group, the interested isocyanate or thioisocyanate and 1 drop of DIEA in DCM were added to the resin and allowed to react for 3 hours. The resin was washed five times with DMF, once with isopropanol, five times with DCM. The resin was dried in vacuo overnight.

The compound was cleaved from the resin by treatment of the resin with 95% TFA/2.5% TIS/2.5% water at room temperature for 90 min. After filtration and evaporation, ice cold ether was added to the residue. The resultant precipitate was isolated by centrifugation and washed three times with ether. The precipitate was subjected to preparative HPLC to yield the compounds of Formulas (26), (27), (28), (29), (33), (44), (46), (50), (51), (52), (55), (62), (63), (64), (65), (69) and (74) were prepared by this method.

Formulas (35), (36), (37), (38), (43) and (51) were prepared by similar method as described above, except that (3S)-Fmoc-3-amino-1-carboxymethyl-caprolactame was used as the starting material instead of Fmoc-D-proline.

B. Boc Strategy

MBHA-resin was washed five times with DCM and three times with DMF. A solution of 2 equivalents of N-carboxymethyl-(S)-3-t-butyloxycarbonylamino-homopiperidine, 2 equivalent of HOBt (1.0 mmol), and 2 equivalent of DIC (1.0 mmol) in 5 mL of DMF was added to the resin and allowed to react for 4 h. The solution was drained by filtration and the resin was washed three times with DMF, three times with DCM, once with 2-propanol, and three times with DCM. The coupling of amino acid to the resin was then checked by standard Kaiser's test. The resin was treated with TFA/anisole/DCM: 25/5/70 for 2 min. The solution was drained by filtration and the resin was treated again with TFA/anisole/DCM: 25/5/70 for 30 min. The resin was washed three times with DCM, once with 2-propanol, once with DCM, once with 2-propanol, once with DCM, once with 2-propanol, and three times with DCM. The resin was treated three times with 10% DIEA in DCM for 2 min. The solution was drained by filtration and the resin was washed three times with DCM and three times with DMF.

The above cycle was iterated for each subsequent amino acid. After completion of the desired sequence and removal of the last Boc-group, 4-(N'-(o-tolyl)urea)phenyl acetic acid or 4-(N'-(2-pyridyl)urea)phenyl acetic acid (which were prepared as described above) was coupled to the free N-terminus and the resin was washed as described above. The resin was dried *in vacuo* over KOH and the peptide was cleaved from the resin as follows:

The resin (0.1 meq) was placed in a teflon reaction vessel and anisole (0.2 mL) was added as a scavenger. For methionine-containing compound, methyl

sulfide (0.2 mL) was included in the reaction mixture. The reaction vessel was flushed with nitrogen and cooled to -78°C. HF (approximately 5mL) was condensed into the vessel, and the mixture was stirred for 1 h at 0°C. HF was evaporated by flushing with nitrogen, and the vessel containing the resin was dried in vacuo over KOH. The resin was washed three times with TFA (2 mL) and filtered. The combined filtrates were concentrated in vacuo to approximately 0.5 mL and cooled to °C. Ice cold ether (10 mL) was added and the precipitate was isolated by centrifugation and washed three times with ether. The precipitates were dried in vacuo and subjected to preparative HPLC to give compounds of the Formulas (70), (71), (72), (73) and (78).

Syntheis of VLA-4 antagonist ester prodrugs:

Most ester prodrugs were synthesized by esterification of the side chain carboxyl group of aspartic acid in the molecules. For example, VLA-4 antagonists were reacted with different alcohols to form ester prodrugs after purification on preparative HPLC or preparative TLC. The typical procedure was as follows:

To a solution of Formula (54) (120mg, 0.16mmol), and EtOH (30 mg, 0.65 mmol) in DCM was added EDC (37 mg, 0.19 mmol) and DMAP (2 mg, 0.016 mmol) and stirred overnight. The reaction mixture was washed with saturated $NaHCO_3$, H_2O and brine then dried over Na_2SO_4. The solution was evaporated and the residue was purified by preparative HPLC (5-58% B over 45 min; Flow rate: 15 ml/min) to give the compound of the Formula (84) (50 mg).

The compounds of Formulas (85), (86), (88), (89), (90), (91), (92), (93) and (94) were preparared by using the above method.

The compounds of Formulas (95), (96), (97) and (98) were also prepared by using this method, utilizing Formulas (43) and (77) as the starting materials were used instead of Formula (54).

In addition to the esterification from alcohol, there is another protocol used in which alkyl halide was treated with carboxyl group in the presence of base. Thus the -N,N,-dimethylaminoacetyl ester of Formula (54), (i.e. Formula (87) was prepared by reacting Formula (54) with 2-chloro-N,N,-dimethylacetamide in the compound was subjected to the presence of NaI and DIEA in DMF overnight. Preparative TLC purification (12% MeOH/DCM) was used to give the compound of Formula (87).

The compound of Formulas (84) and (99) are all benzyl esters which can be synthesized in a manner to the compounds above.

TABLE 1

Formula	Mass Spec. (m/z)	HPLC time and gradient	Instrument
(14)	729(MH+), 727(MH-)	32.5 min; 5-90%B/45 min	Beckman
(15)	715(MH+)	17.3 min; 5-90%B/25 min	Beckman
(16)	714(MH+)	17.3 min; 5-90%B/25 min	Beckman
(17)	745(MH+)	17.9 min; 5-90%B/25 min	Beckman
(18)	743(MH+), 741(MH-)	20.0 min; 5-90%B/35 min	Beckman
(21)	712(MH-)	17.4 min; 5-90%B/25 min	Beckman
(22)	730(MH+), 728(MH-)	18.7 min; 5-90%B/25 min	Beckman
(25)	699(MH+), 697(MH-)	21.7 min; 5-90%B/25 min	Beckman
(26)	742(MH+), 740(MH-)	24.5 min; 5-90%B/45 min	Beckman
(27)	756(MH+), 754(MH-)	24.0 min; 5-90%B/45 min	Beckman
(28)	756(MH+), 754(MH-)	25.2 min; 5-90%B/45 min	Beckman
(29)	776(MH+), 774(MH-)	22.1 min; 5-90%B/35 min	Beckman
(30)	744(MH+), 742(MH-)	13.2 min; 30-70%B/45 min	Beckman
(31)	745(MH+), 743(MH-)	21.2 min; 30-70%B/45 min	Beckman
(32)	743(MH+), 741(MH-)	19.3 min; 5-90%B/25 min	Beckman

Formula	Mass Spec. (m/z)	HPLC time and gradient	Instrument
(33)	794(MNa+), 770(MH-)	17.0 min; 5-80%B/25 min	Gilson
(34)	799.4(MNa+), 775(MH-	31.0 min; 15-60%B/45 min	Beckman
(35)	694(MH+), 692(MH-)	23.2 min; 5-70%B/35 min	Beckman
(36)	696(MH+), 694(MH-)	16.0 min, 5-90%B/25 min	Gilson
(37)	666(MH+), 664(MH-)	15.7 min, 5-90%B/25 min	Gilson
(38)	700(MH+), 698(MH-)	16.6 min, 5-90%B/25 min	Gilson
(39)	665(MH+), 663(MH-)	29.0 min; 15-60%B/45 min	Beckman
(40)	714(MH+), 712(MH-)	25.8 & 26.0min; 15-60%B/45	Beckman
(41)	757(MH+), 755(MH-)	13.5 min; 5-90%B/25 min	Beckman
(42)	743(MH+)	13.5 min; 5-90%B/25 min	Beckman
(43)	680(MH+), 678(MH-)	18.5 min; 5-65%B/25 min	Beckman
(44)	758(MH+), 756(MH-)	20.5 min; 5-90%B/35 min	Beckman
(45)	741(MH+), 739(MH-)	24.3 min; 30-70%B/45 min	Beckman
(46)	817(MNa+), 793(MH-)	18.9 min; 5-80%B/25 min	Gilson
(47)	651(MH+), 649(MH-)	26.0 min; 15-60%B/45 min	Beckman

Formula	Mass Spec. (m/z)	HPLC time and gradient	Instrument
(48)	757(MH+), 755(MH-)	16.5 min; 30-70%B/45 min	Beckman
(49)	786(MH+), 784(MH-)	17.2 min; 5-80%B/25 min	Beckman
(50)	722(MH+), 720(MH-)	18.7 min; 5-80%B/25 min	Gilson
(51)	784(MNa+), 760(MH-)	18.2 min; 5-80%B/25 min	Gilson
(52)	762(MNa+), 738(MH-)	17.8 min; 5-80%B/25 min	Gilson
(53)	742(MH+), 740(MH-)	16.5 min; 5-90%B/25 min	Beckman
(54)	756(MH+), 754(MH-)	16.7 min; 5-90%B/25 min	Beckman
(55)	756(MH+), 754(MH-)	21.2 min; 5-90%B/35 min	Beckman
(56)	695(MH+)	22.2 min; 5-70%B/25 min	Beckman
(57)	786(MH+), 784(MH-)	16.5 min; 5-80%B/25 min	Beckman
(58)	730(MH+), 728(MH-)	20.0 min; 5-90%B/35 min	Beckman
(59)	804(MH+), 802(MH-)	23.4 min; 5-90%B/35 min	Beckman
(60)	800(MH+), 798MH-)	20.8 min; 5-90%B/35 min	Gilson
(61)	721(MH+), 719(MH-)	21.5 min; 5-90%B/35 min	Beckman
(62)	774(MH+), 772(MH-)	20.3 min; 5-90%B/35 min	Beckman

Formula	Mass Spec. (m/z)	HPLC time and gradient	Instrument
(63)	790 (MH+), 788 (MH-)	20.5 min; 5-90%B/35 min	Beckman
(64)	730 (MH+), 728 (MH-)	18.1 min; 5-90%B/35 min	Beckman
(65)	796 (MH+), 794 (MH-)	23.1 min; 5-90%B/35 min	Beckman
(66)	730 (MH+), 728 (MH-)	14.2 min; 5-90%B/25 min	Beckman
(67)	758 (MNa+), 734 (MH-)	17.7 min; 5-90%B/25 min	Beckman
(68)	685 (MH+), 683 (MH-)	21.8 min; 5-90%B/25 min	Beckman
(69)	726 (MH+)	21.5 min; 5-80%B/25 min	Gilson
(70)	684 (MH+) 682 (MH-)	19.9 min; 5-50%B/25 min	Beckman
(71)	706 (MH+), 704 (MH-)	24.3 min; 5-50%B/25 min	Beckman
(72)	653 (MH+), 651 (MH-)	14.9 min; 5-50%B/25 min	Beckman
(73)	666 (MH+), 664 (MH-)	20.7 min; 5-50%B/25 min	Beckman
(74)	700 (MH+), 698 (MH-)	18.4 min; 5-90%B/35 min	Beckman
(75)	771 (MH-)	18.8 min; 5-90%B/25 min	Beckman
(76)	666 (MH+), 664 (MH-)	21.3 min; 15-60%B/45 min	Beckman
(77)	680 (MH+), 678 (MH-)	24.3 min; 15-60%B/45 min	Beckman

Formula	Mass Spec. (m/z)	HPLC time and gradient	Instrument
(78)	640(MH+), 638(MH-)	16.8 min; 5-50%B/25 min	Beckman
(79)	708(MH+), 706(MH-)	25.8 min; 15-60%B/45 min	Beckman
(83)	784(MH+)	18.2 min; 5-90%B/25 min	Beckman
(84)	846(MH+)	19.6 min; 5-90%B/25 min	Beckman
(85)	863(MH+)	17.9 min; 5-90%B/25 min	Gilson
(86)	847(MH+)	15.8 min; 5-90%B/25 min	Beckman
(87)	841(MH+)	17.5 min; 5-90%B/25 min	Gilson
(88)	827(MH+)	16.9 min; 5-90%B/25 min	Beckman
(89)	902(MH+)	17.8 min; 5-90%B/25 min	Beckman
(90)	770(MH+)	17.8 min; 5-90%B/25 min	Beckman
(91)	852(MH+)	19.9 min; 5-90%B/25 min	Gilson
(92)	798(MH+)	18.6 min; 5-90%B/25 min	Beckman
(93)	826(MH+)	20.2 min; 5-90%B/25 min	Beckman
(94)	826(MH+)	19.9 min; 5-90%B/25 min	Beckman
(95)	708(MH+)	16.5 min; 5-90%B/25 min	Beckman

Formula	Mass Spec. (m/z)	HPLC time and gradient	Instrument
(96)	722(MH+), 720(MH-)	17.2 min; 5-90%B/25 min	Beckman
(97)	750(MH+), 748(MH-)	18.8 min; 5-90%B/25 min	Beckman
(98)	708(MH+)	16.9 min; 5-90%B/25 min	Beckman
(99)	770(MH+), 768(MH-)	18.7 min; 5-90%B/25 min	Beckman

EXAMPLE 2

Assay for VLA-4 Binding Inhibition

Jurkat cells (ATCC TIB 152), a human T lymphoblastic line, labeled with Europium were used to assay *in vitro* binding inhibition by compounds discussed herein. Jurkat cells were washed twice with phosphate buffered saline at 37°C and resuspended in 1 ml of labeling buffer (labeling buffer was made up in 50 mM HEPES pH 7.4, 93 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$ containing 2.5 mM DTPA, 0.5 mM $EuCl_3$, 0.1 mg/ml dextran sulfate). Cells were incubated in labeling buffer for 30 min at 4°C. After 30 min, cells were further incubated with 30 µl of 100 mM $CaCl_2$, for 5 min at 4°C. Eu-labeled cells were then washed sequentially at 4°C twice with RPMI cell culture medium supplemented with 10 mM glucose and 2 mM Ca Cl_2, once with PBS supplemented with 1 mM EDTA and finally once with RPMI supplemented with 1% bovine serum albumin (RPMI/1% BSA). Prior to adhesion assays on CS-1 coated plates Jurkat cells were resuspended in RPMI/ 1% BSA at $1x10^6$ cell/ml.

Plates (96-well clusters) were coated with 50µl of a solution of 1µg/ml CS-1 25-amino acid peptide in 0.1 M Na_2CO_3, pH 9.5 containing 10 µg/ml BSA and allowed to dry out overnight by incubation at 37°C. Additional surface binding sites blocked with RPMI/1% BSA for 2 hr at room temperature. Finally, plates were washed twice with PBS, pH 7.4.

Eu-labeled cells were preincubated with inhibitor compound for 30 min at room temperature and then the cell mixture was added to CS-1-coated wells for adhesion assays for 30 min at 37°C. Non-adherent cells were washed off 3 times with RPMI/1% BSA. Cells that had adhered to CS-1 were lysed with 0.5% SDS. Released Eu from adherent cells was complexed with Enhancing solution and analyzed for fluorescence on a fluorometer (1232 DELFIA-WALLAC, Turku, Finland) to quantitate inhibition of adhesion.

Exemplary compounds that inhibit VLA-4 binding are set forth in Table 2.

TABLE 2

Formula Number	Potency IC_{50} (nM)
(14)	0.4
(15)	3.2
(16)	47
(17)	3.2
(18)	1.5
(21)	94
(22)	166
(25)	2015
(26)	4.4
(27)	42
(28)	0.3
(29)	4.9
(30)	5.6
(31)	2.0
(32)	4102
(33)	1.2
(34)	0.3
(35)	1.6
(36)	3.0
(37)	4.5
(38)	1.1
(39)	4.7
(40)	1.2
(41)	53
(42)	4.3

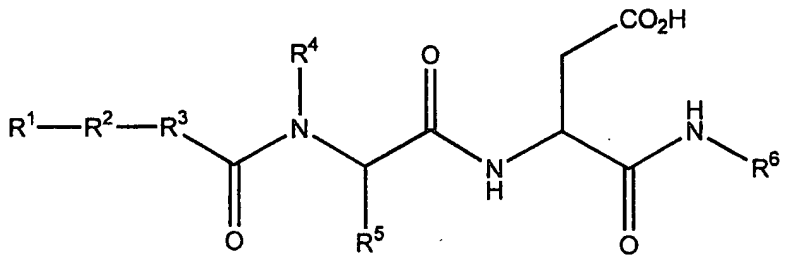
Formula Number	Potency IC_{50} (nM)
(43)	0.2
(44)	80
(45)	10
(46)	2.3
(47)	3.0
(48)	3.7
(49)	0.7
(50)	1.7
(51)	1.6
(52)	3.4
(53)	1.0
(54)	0.9
(55)	0.3
(56)	1225
(57)	2.9
(58)	44
(59)	5.4
(60)	0.3
(61)	602
(62)	1.1
(63)	10
(64)	1.4
(65)	1.2
(66)	13
(67)	137
(68)	125
(69)	2.1
(70)	0.9

Formula Number	Potency IC_{50} (nM)
(71)	0.2
(72)	47
(73)	1.4
(74)	19
(75)	4444
(76)	1.3
(77)	2.1
(78)	14
(79)	6.3

Although the invention has been described with reference to the presently preferred embodiments, it should be understood that various modifications can be made by those skilled in the art without departing from the invention. Accordingly, the invention is set out in the following claims.

WE CLAIM:

1. A compound comprising Formula (1):

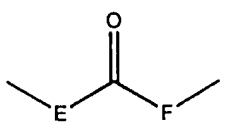


(1)

wherein:

R^1 is an alkyl group, an adamantyl group, or a 5-, 6-, 6,5-, or 6,6-membered non-heterocyclic, heterocyclic, aromatic, partially saturated or fully saturated ring that is optionally substituted by one or more nitro, fluoro, chloro, bromo, amino, lower alkylamino, di(lower alky)amino, hydroxy, lower alkyl, lower alkoxy, alkylcarbonyloxy, alkylcarbonylamino, alkylcarbonyl, or lower alkoxycarbonyl groups and when R^1 is such a ring, the ring is connected to R^2 either directly by a bond or indirectly through a lower alkyl group;

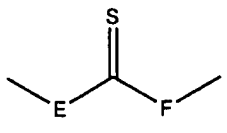
R^2 is a lower alkyl, a C_2 to C_4 alkenyl, or a C_2 to C_4 alkynyl group, in which each group optionally can contain a carbonyl, ether, thioether, aminocarbonyl, sulfonamido, sulfone, or sulfoxide group; or R^2 can be a group of the Formula (2):



(2)

;

or of the Formula (3):



(3)

;

E is a CX^1X^2 group, a NX^3 group or an oxygen atom and F is a CX^4X^5 group, a NX^6 group or an oxygen atom;

X^1, X^2, X^3, X^4, X^5, and X^6 are independently selected from the group consisting of a hydrogen atom or a lower alkyl group with the provisos that:

E and F both are not simultaneously oxygen atoms; and,

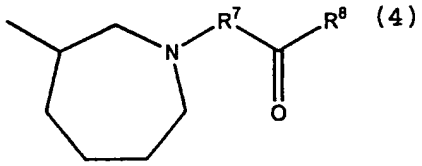
if R^1 is the alkyl group, R^2 must be a group of the Formula (2) or (3);

R^3 is a 5-, 6-, 6,5-, or 6,6-membered aromatic ring optionally containing from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen or sulfur atoms and is connected to the carbonyl carbon of the amide bond containing R^4 of Formula 1 either directly by a bond or indirectly through a lower alkyl group;

R^4 is a hydrogen atom or a lower alkyl group;

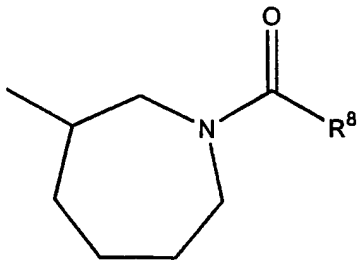
R^5 is hydrogen, a lower alkyl, or a lower alkyl amido group optionally substituted by a lower alkyl amido group, lower hydroxyalkyl, di(lower alkyl)sulfide, or lower thioalkyl group, or a 5- or 6-membered non-heterocyclic saturated ring connected to the methinyl carbon of Formula 1 either directly by a bond or indirectly through a lower alkyl group;

R^6 is a group of the Formula (4):



(4)

or Formula (5):



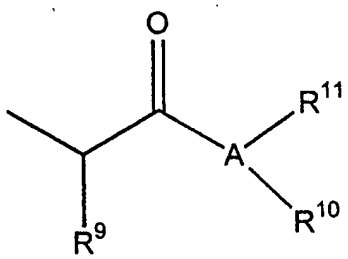
(5)

wherein:

R^7 is a lower alkyl group;

R^8 is a lower alkyl, an amino, a loweralkylamino, or a di(loweralkyl)amino group; or

R^6 is a group of the Formula (6):

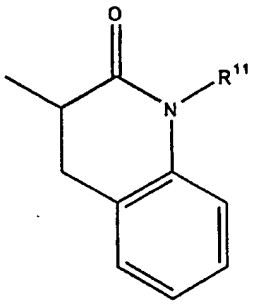


(6)

wherein:

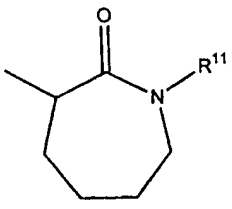
A is a nitrogen or oxygen atom;

when A is a nitrogen atom, R^9 is a hydrogen atom or a lower alkyl, lower hydroxyalkyl, lower thioalkyl, di(lower alkyl) sulfide; a 6-membered non-heterocyclic aromatic, partially saturated or saturated ring or a 5-or 6-membered heterocyclic aromatic ring containing from 1 to 3 nitrogen, oxygen or sulfur atoms, or a 3-indolyl ring; each of these rings is connected to the methinyl carbon of Formula 6 either directly by a bond or indirectly through a lower alkyl group; the non-heterocyclic or heterocyclic aromatic ring at R^9 can optionally be substituted by a hydroxy, nitro, primary carboxamide, lower alkyl primary carboxamide, or (lower alkoxy)lower alkyl group; or R^9 can be taken together with R^{10} to form a 6,6-membered ring of the Formula (7):



(7)

or a group of the Formula (8):



(8)

when A is a nitrogen atom in Formula 6, R^{10} can be a lower alkyl, a lower hydroxyalkyl, or a N-morpholino group; or R^{10} can be taken together with R^9 as described above, or taken together with R^{11} to form a 5- or 6-membered heterocyclic ring containing 1 or 2 nitrogen atoms and optionally containing an oxygen atom, a sulfur atom, a sulfone group or a sulfoxide group wherein the heterocyclic ring is aromatic, partially saturated or fully saturated; the 5- or 6-membered heterocyclic ring optionally can be substituted by one or more hydroxy, lower alkyl, lower hydroxyalkyl, lower alkoxy, lower hydroxyalkoxy lower alkyl, (lower alkoxy)lower alkyl, alkylcarbonyl, carboxylic acid, primary carboxamide, lower alkyl carboxylic acid, lower alkyl primary carboxamide, lower alkylcarbonyloxy, phenyl, phenyl lower alkylsulfonyl, or phenylsulfonyl groups in which the phenyl group of the phenyl lower alkyl sulfonyl or phenyl sulfonyl group is optionally substituted by a lower alkyl moiety;

when A is a nitrogen atom in Formula 6, R^{11} is a lower alkyl optionally substituted by one or more (lower alkyl) amino, or di(lower alkyl) amino, lower alkyl primary carboxamide, lower alkyl substituted by a morpholino group, a cyclohexyl group, a hydrogen atom or is taken together with R^{10} as described above;

when A is an oxygen atom in Formula 6, R^9 is as above except that the R^9 cannot be taken with R^{10};

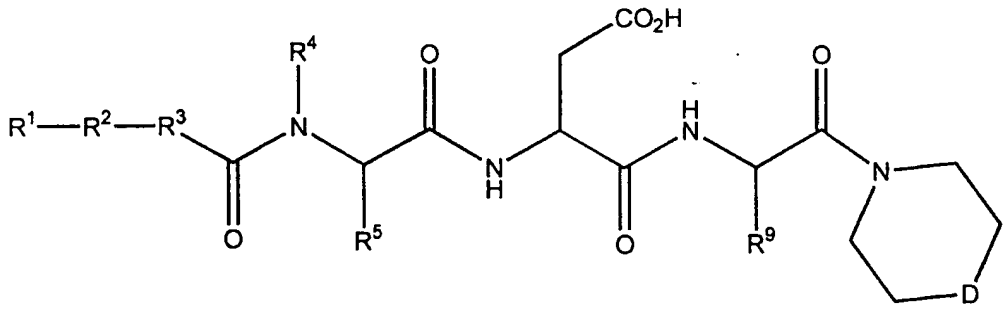
when A is an oxygen atom in Formula 6, R^{10} is a lower alkyl or a 6-membered non-heterocyclic or heterocyclic ring that is aromatic, partially saturated, or saturated and is connected directly to the methinyl carbon of Formula 6 by a bond or indirectly through a lower alkyl group; and

when A is an oxygen atom in Formula 6, R^{11} is absent; or

a pharmaceutically-acceptable salt therof.

2. A compound of claim 1 comprising the following Formula (9):

(9)



wherein:

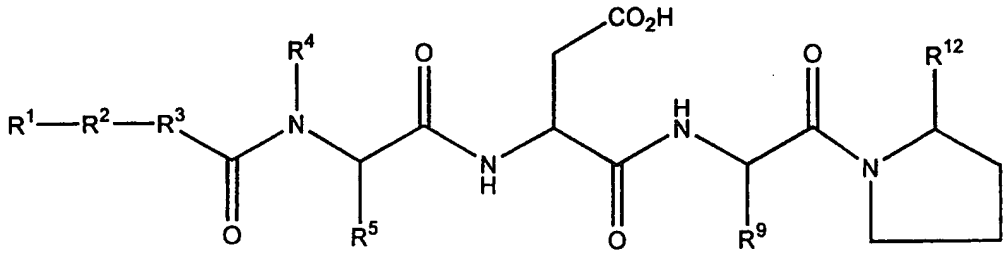
D is an oxygen or sulfur atom or a sulfone, sulfoxide, CH_2, or NH group and the CH_2 or NH group can be optionally substituted by a lower alkyl, primary carboxamide, lower alkyl primary carboxamide, hydroxy, lower hydroxyalkyl, lower hydroxyalkoxy lower alkyl, carboxylic acid, lower alkyl carboxylic acid, phenyl, phenylsulfonyl in which the phenyl group of the phenyl lower alkyl sulfonyl or phenyl sulfonyl group is optionally substituted by a lower alkyl, or a lower alkylcarbonyloxy group;

R^9 is a hydrogen atom or a lower alkyl, lower hydroxyalkyl, lower thioalkyl, di(lower alkyl) sulfide; a 6-membered non-heterocyclic aromatic, partially saturated

or saturated ring or a 5-or 6-membered heterocyclic aromatic ring containing from 1 to 3 nitrogen, oxygen or sulfur atoms, or a 3-indolyl ring; each of these rings is connected to the methinyl carbon of Formula 9 either directly by a bond or indirectly through a lower alkyl group; and the non-heterocyclic or heterocyclic aromatic ring at R^9 can optionally be substituted by a hydroxy, nitro, primary carboxamide, lower alkyl primary carboxamide, or (lower alkoxy)lower alkyl group.

3. A compound of claim 1 comprising the following Formula (10):

(10)



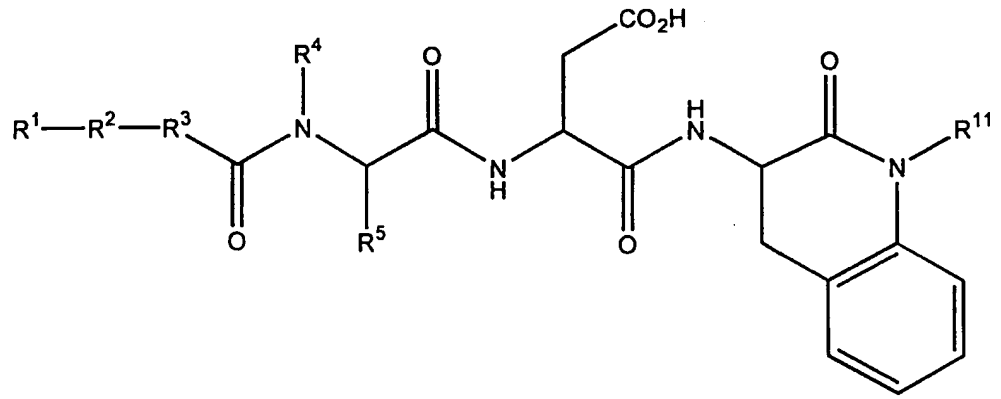
wherein:

R^9 is a hydrogen atom or a lower alkyl, lower hydroxyalkyl, lower thioalkyl, di(lower alkyl) sulfide; a 6-membered non-heterocyclic aromatic, partially saturated or saturated ring or a 5-or 6-membered heterocyclic aromatic ring containing from 1 to 3 nitrogen, oxygen or sulfur atoms, or a 3-indolyl ring; each of these rings is connected to the methinyl carbon of Formula 10 either directly by a bond or indirectly through a lower alkyl group; the non-heterocyclic or heterocyclic aromatic ring at R^9 can optionally be substituted by a hydroxy, nitro, primary carboxamide, lower alkyl primary carboxamide, or (lower alkoxy)lower alkyl group; and

R^{12} is a hydrogen atom, carboxylic acid, a lower alkyl carboxylic acid, a primary carboxamide, a lower alkyl primary carboxamide, a lower alkyl group or a lower hydroxyalkyl.

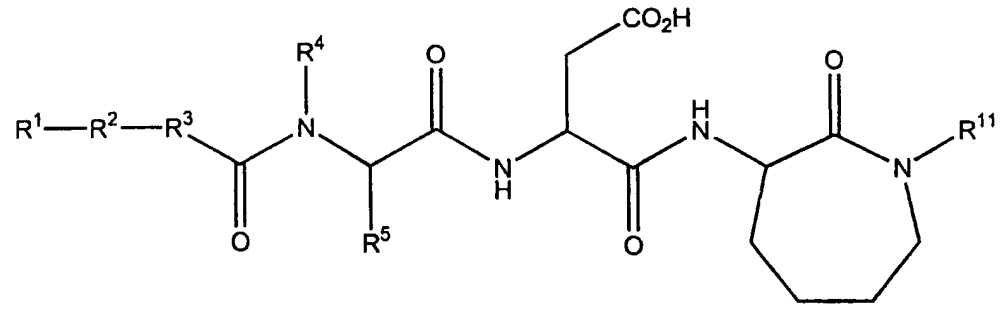
4. A compound of claim 1 comprising the following Formula (11):

(11)



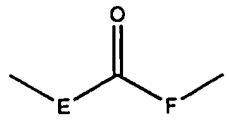
5. A compound of claim 1 comprising the following Formula (12):

(12)



6. The compound of claim 1, wherein R^1 is a 5-, 6-, 6,5-, or 6,6-membered non-heterocyclic, heterocyclic, aromatic, partially saturated or fully saturated ring that is optionally substituted by one or more nitro, fluoro, chloro, bromo, amino, lower alkylamino, di(lower alkyl)amino, hydroxy, lower alkyl, lower alkoxy, alkylcarbonyloxy, alkylcarbonylamino, alkylcarbonyl, or lower alkoxycarbonyl groups and the ring is connected to R^2 either directly by a bond or indirectly through a lower alkyl group.

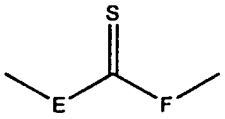
7. The compound of claim 1, wherein R^2 is a group of the Formula (2):



(2)

;

or of the Formula (3):



(3)

;

wherein:

E is a CX^1X^2 group, a NX^3 group or an oxygen atom and F is a CX^4X^5 group, a NX^6 group or an oxygen atom; and

X^1, X^2, X^3, X^4, X^5, and X^6 are independently selected from the group consisting of a hydrogen atom or a lower alkyl group with the provisios that:

E and F both are not simultaneously oxygen atoms; and

if R^1 is the alkyl group, R^2 must be a group of the Formula (2) or (3).

8. The compound of claim 1, wherein R^3 is a 6-membered aromatic ring optionally containing from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen or sulfur atoms and is connected to the carbonyl carbon of the amide bond containing R^4 of Formula 1 either directly by a bond or indirectly through a lower alkyl group.

9. The compound of claim 1, wherein R^4 is a hydrogen atom.

10. The compound of claim 1, wherein R^5 is hydrogen, a lower alkyl, or a lower alkyl amido group group or or a 6-membered non-heterocyclic saturated ring that is connected to the methinyl carbon of Formula 1 either directly by a bond or indirectly through a lower alkyl group.

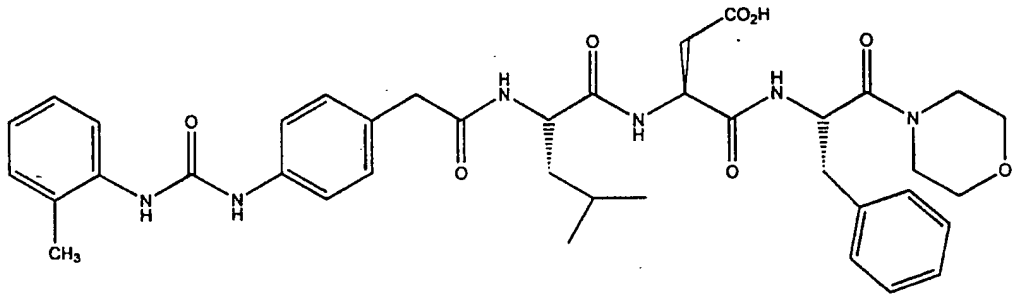
11. The compound of claim 1, wherein R^9 is the 6-membered non-heterocyclic aromatic, partially saturated or saturated ring or the 5-or 6-membered heterocyclic aromatic ring containing from 1 to 3 nitrogen, oxygen or sulfur atoms, or a 3-indolyl ring; each of these rings is connected to the methinyl carbon of Formula 9 either directly by a bond or indirectly through a lower alkyl group; and the non-heterocyclic or heterocyclic aromatic ring at R^9 can optionally be substituted by a hydroxy, nitro, primary carboxamide, lower alkyl primary carboxamide, or (lower alkoxy)lower alkyl group.

12. The compound of claim 1, wherein A is the nitrogen atom and R^{10} is taken together with R^{11} to form a 5- or 6-membered heterocyclic ring containing 1 or 2 nitrogen atoms and optionally containing an oxygen atom, a sulfur atom, a sulfone group or a sulfoxide group wherein the heterocyclic ring is aromatic, partially saturated or fully saturated; the 5- or 6-membered heterocyclic ring optionally can be substituted by one or more hydroxy, lower alkyl, lower hydroxyalkyl, lower akoxy, lower hydroxyalkoxy lower alkyl, (lower alkoxy)lower alkyl, alkylcarbonyl, carboxylic acid, lower alkyl carboxylic acid, primary carboxamide, lower alkyl primary carboxamide, lower alkylcarbonyloxy, phenyl lower alkylsulfonyl, or phenylsulfonyl groups in which the phenyl group of the phenyl lower alkyl sulfonyl or phenyl sulfonyl group is optionally substituted by a lower alkyl moiety.

13. The compound of claim 3, wherein R^{12} is a primary carboxamide group and the carbon atom (a) forms the D isomer.

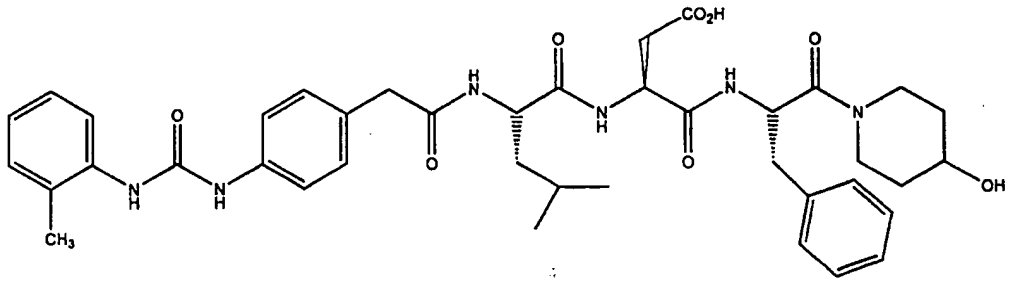
14. The compound of claim 1 comprising the following Formula (14):

(14)



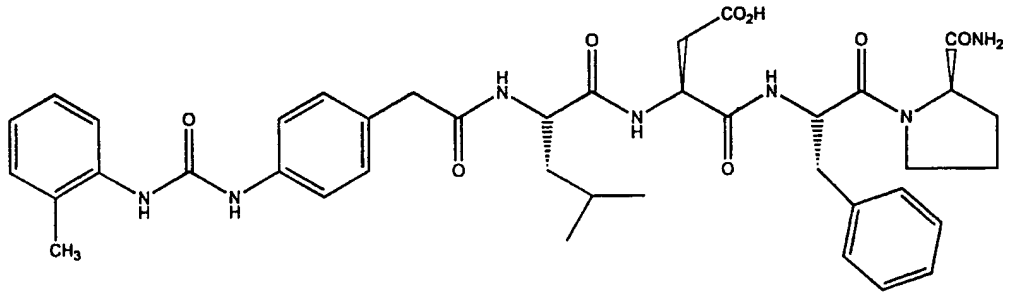
15. The compound of claim 1 comprising the following Formula (18):

(18)



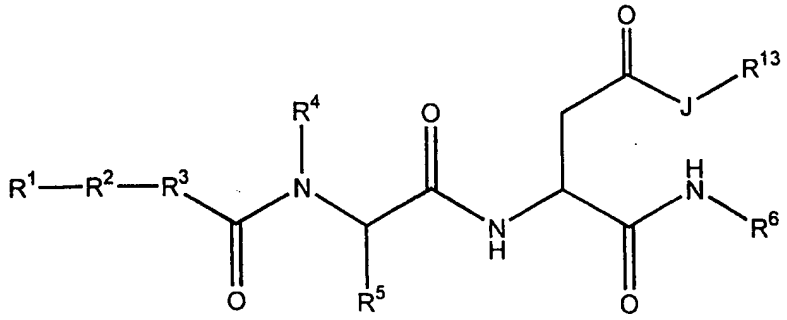
16. The compound of claim 1 comprising the following Formula (28):

(28)



17. A pharmaceutically-acceptable derivative of the following Formula (80):

(80)

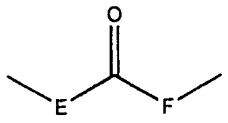


wherein:

J is an oxygen or a sulfur atom;

R^1 is an alkyl group, an adamantyl group, or a 5-, 6-, 6,5-, or 6,6-membered non-heterocyclic, heterocyclic, aromatic, partially saturated or fully saturated ring that is optionally substituted by one or more nitro, fluoro, chloro, bromo, amino, lower alkylamino, di(lower alkyl)amino, hydroxy, lower alkyl, lower alkoxy, alkylcarbonyloxy, alkylcarbonylamino, alkylcarbonyl, or lower alkoxycarbonyl groups and when R^1 is such a ring, the ring is connected to R^2 either directly by a bond or indirectly through a lower alkyl group;

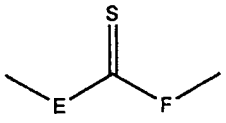
R^2 is a lower alkyl, a C_2 to C_4 alkenyl, or a C_2 to C_4 alkynyl group, in which each group optionally can contain a carbonyl, ether, thioether, aminocarbonyl, sulfonamido, sulfone, or sulfoxide group; or R^2 can be a group of the Formula (2):



(2)

;

or of the Formula (3):



(3)

;

E is a CX^1X^2 group, a NX^3 group or an oxygen atom and F is a CX^4X^5 group, a NX^6 group or an oxygen atom;

X^1, X^2, X^3, X^4, X^5, and X^6 are independently selected from the group consisting of a hydrogen atom or a lower alkyl group with the provisos that:

E and F both are not simultaneously oxygen atoms; and,

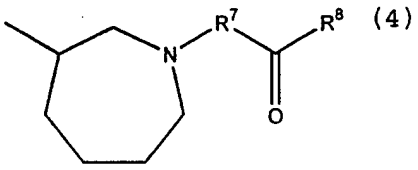
if R^1 is the alkyl group, R^2 must be a group of the Formula (2) or (3);

R^3 is a 5-, 6-, 6,5-, or 6,6-membered aromatic ring optionally containing from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen or sulfur atoms and is connected to the carbonyl carbon of the amide bond containing R^4 of Formula 1 either directly by a bond or indirectly through a lower alkyl group;

R^4 is a hydrogen atom or a lower alkyl group;

R^5 is hydrogen, a lower alkyl, or a lower alkyl amido group optionally substituted by a lower alkylamido group, lower hydroxyalkyl, di di(lower alkyl)sulfide, or lower thioalkyl group, or a 5- or 6-membered non-heterocyclic saturated ring connected to the methinyl carbon of Formula 1 either directly by a bond or indirectly through a lower alkyl group;

R^6 is a group of the Formula (4):

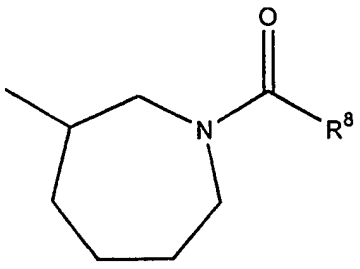


(4)

;

or Formula (5):

(5)

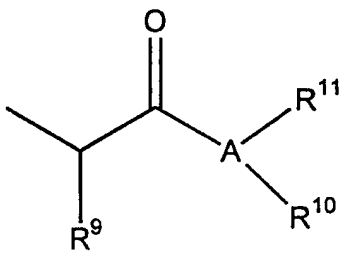


wherein:

R^7 is a lower alkyl group;

R^8 is a lower alkyl, an amino, a loweralkylamino, or a di(loweralkyl)amino group; or

R^6 is a group of the Formula (6):



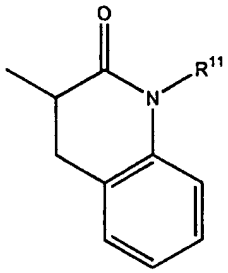
(6)

wherein:

A is a nitrogen or oxygen atom;

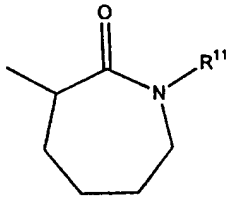
when A is a nitrogen atom, R^9 is a hydrogen atom or a lower alkyl, lower hydroxyalkyl, lower thioalkyl, di(lower alkyl) sulfide; a 6-membered non-heterocyclic aromatic, partially saturated or saturated ring or a 5-or 6-membered heterocyclic aromatic ring containing from 1 to 3 nitrogen, oxygen or sulfur atoms, or a 3-indolyl ring; each of these rings is connected to the methinyl carbon of Formula 6 either directly by a bond or indirectly through a lower alkyl group; the non-heterocyclic or heterocyclic aromatic ring at R^9 can optionally be substituted by a hydroxy, nitro, primary carboxamide, lower alkyl primary carboxamide, or (lower alkoxy)lower alkyl group; or R^9 can be taken together with R^{10} to form a 6,6-membered ring of the Formula (7):

(7)



or a group of the Formula (8):

(8)



;

when A is a nitrogen atom in Formula 6, R^{10} can be a lower alkyl, a lower hydroxyalkyl, or a N-morpholino group; or R^{10} can be taken together with R^9 as described above, or taken together with R^{11} to form a 5- or 6-membered heterocyclic ring containing 1 or 2 nitrogen atoms and optionally containing an oxygen atom, a sulfur atom, a sulfone group or a sulfoxide group wherein the heterocyclic ring is aromatic, partially saturated or fully saturated; the 5- or 6-membered heterocyclic ring optionally can be substituted by one or more hydroxy, lower alkyl, lower hydroxyalkyl, lower alkoxy, lower hydroxyalkoxy lower alkyl, (lower alkoxy)lower alkyl, alkylcarbonyl, carboxylic acid, lower alkyl carboxylic acid, primary carboxamide, lower alkyl primary carboxamide, lower alkylcarbonyloxy, phenyl, phenyl lower alkylsulfonyl, or phenylsulfonyl groups in which the

phenyl group of the phenyl lower alkyl sulfonyl or phenyl sulfonyl group is optionally substituted by a lower alkyl moiety;

when A is a nitrogen atom in Formula 6, R^{11} is a lower alkyl optionally substituted by one or more (lower alkyl) amino, or di(lower alkyl) amino groups, lower alkyl primary carboxamide, lower alkyl substituted by a morpholino group, a cyclohexyl group, a hydrogen atom or is taken together with R^{10} as described above;

when A is an oxygen atom in Formula 6, R^{9} is as above except that the R^{9} cannot be taken with R^{10};

when A is an oxygen atom in Formula 6, R^{10} is a lower alkyl or a 6-membered non-heterocyclic or heterocyclic ring that is aromatic, partially saturated, or saturated and is connected directly to the methinyl carbon of Formula 6 by a bond or indirectly through a lower alkyl group;

when A is an oxygen atom in Formula 6, R^{11} is absent; and

R^{13} is:

a) a lower alkyl that is optionally substituted by a hydroxyl, cyclohexyl, phenyl, phenyl sulfonyl, pridinyl, pyridinyl N-oxide, a (lower alkyl) amino, a di(lower alkyl) amino, a (lower alkyl) amide, a di(lower alkyl) amide, a di(lower alkyl)sulfide, a (lower alkoxy)lower alkyl, a ((lower alkoxy)lower alkoxy)lower alkyl a (((lower alkoxy) lower alkoxy)lower alkoxy)lower alkyl, (lower alkylcarbonyloxy)lower alkyl, (N-(lower alkyl)aminocarbonyl)lower alkyl, a ((N-(lower alkyl))(N-(lower alkoxy))amino-carbonyl)lower alkyl, a (N,N-di(lower alkyl)aminocarbonyl)lower alkyl, a

(N'-morpholinocarbonyl)lower alkyl, a (benzyloxycarbonyl)methyl, a 1-((O-((lower alkylcarbonato))eth-1-yl group;

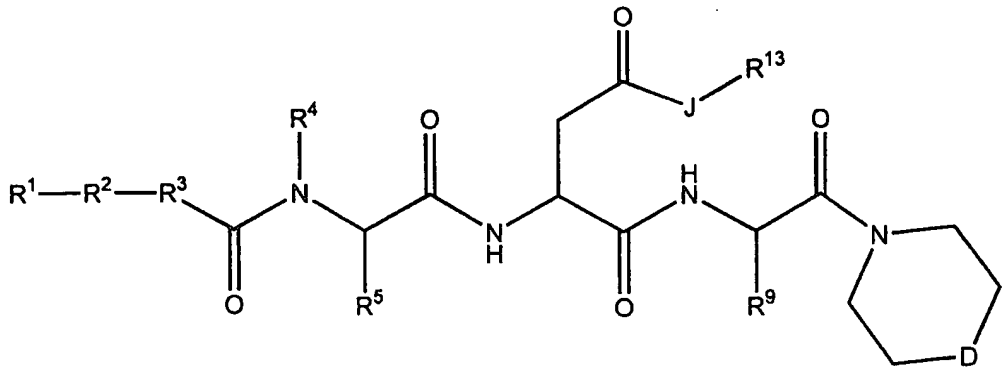
b) a 2-oxo-1,3-dioxolen-4-ylmethyl group;

c) a cyclohexyl, a phenyl, a pyridinyl, a pridinyl N-oxide, a 1,3- dioxan-2-yl, a 3-tetrahydropyranyl, a (4-hydroxybutyric)lacton-3-yl, or a phthalidyl ring, wherein said ring is connected to J either directly by a bond or indirectly by a lower alkyl group; or

a pharmaceutically-acceptable salt thereof.

18. A pharmaceutically-acceptable derivative of claim 17 having the following Formula (81):

(81)



wherein:

D is an oxygen or sulfur atom or a sulfone, sulfoxide, CH_2, or NH group and the CH_2 or NH group can be optionally substituted by a lower alkyl, primary carboxamide, lower alkyl primary carboxamide, hydroxy, lower hydroxyalkyl, lower hydroxyalkoxy lower alkyl, carboxylic acid, lower alkyl carboxylic acid, phenyl, phenyl lower alkyl sulfonyl, phenylsulfonyl in which the phenyl group of the phenyl lower alkyl sulfonyl or phenyl sulfonyl group is optionally substituted by a lower alkyl, or a lower alkylcarbonyloxy group; and

R^9 is a hydrogen atom or a lower alkyl, lower hydroxyalkyl, lower thioalkyl, di(lower alkyl) sulfide; a 6-membered non-heterocyclic aromatic, partially saturated or saturated ring or a 5-or 6-membered heterocyclic aromatic ring containing from 1 to 3 nitrogen, oxygen or sulfur atoms, or a 3-indolyl ring; each of these rings is connected to the methinyl carbon of Formula 81 either directly by a bond or indirectly through a lower alkyl group; and the non-heterocyclic or heterocyclic aromatic

ring at R^9 can optionally be substituted by a hydroxy, nitro, primary carboxamide, lower alkyl primary carboxamide, or (lower alkoxy)lower alkyl group.

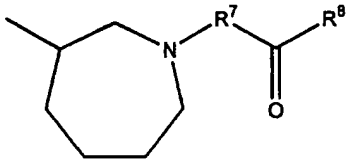
19. A pharmaceutical composition comprising a compound of claim 1 and a carrier.

20. A pharmaceutical composition comprising a pharmaceutically-acceptable derivative of claim 17 and a carrier.

21. The compound of claim 1, wherein

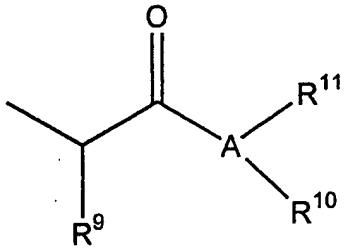
R^6 is a group of the Formula (4); or

(4)



R^6 is a group of the Formula (6):

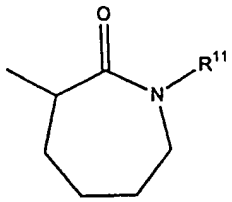
(6)



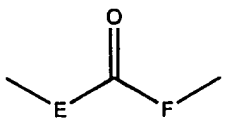
further wherein:

R^9 is taken together with R^{10} to form a group of the Formula (8):

(8)



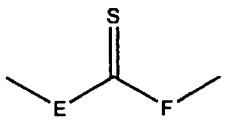
22. The compound of claim 21, wherein R^2 is a group of the Formula (2):



(2)

;

or of the Formula (3):



(3)

;

wherein:

E is a CX^1X^2 group, a NX^3 group or an oxygen atom and F is a CX^4X^5 group, a NX^6 group or an oxygen atom; and

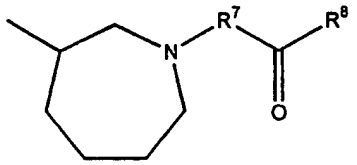
X^1, X^2, X^3, X^4, X^5, and X^6 are independently selected from the group consisting of a hydrogen atom or a lower alkyl group with the provisios that:

E and F both are not simultaneously oxygen atoms; and

if R^1 is the alkyl group, R^2 must be a group of the Formula (2) or (3).

23. A pharmaceutically-acceptable derivative of claim 17, wherein

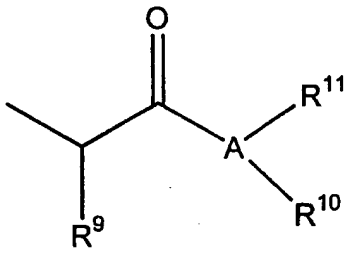
R^6 is a group of the Formula (4):



;

or

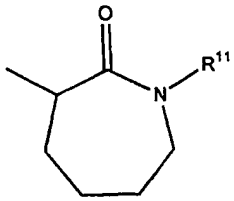
R^6 is a group of the Formula (6):



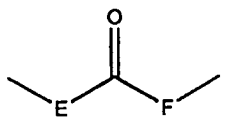
further wherein:

R^9 is taken together with R^{10} to form a group of the Formula (8):

(8)



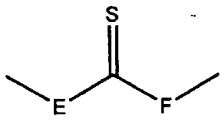
24. A pharmaceutically-acceptable derivative of claim 23 wherein R^2 is a group of the Formula (2):



(2)

;

or of the Formula (3):



(3)

;

wherein:

E is a CX^1X^2 group, a NX^3 group or an oxygen atom and F is a CX^4X^5 group, a NX^6 group or an oxygen atom; and

X^1, X^2, X^3, X^4, X^5, and X^6 are independently selected from the group consisting of a hydrogen atom or a lower alkyl group with the provisios that:

E and F both are not simultaneously oxygen atoms; and

if R^1 is the alkyl group, R^2 must be a group of the Formula (2) or (3).

25. A compound of claim 21 selected from the group of compounds consisting of the Formulas (35), (43), (71), (76), (77), (78), and (79).

26. A pharmaceutically-acceptable derivative of claim 23 selected from the group of compounds consisting of having the Formulas (95), (96), (97), (98), and (99).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/05709

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 562/433, 439, 440, 442, 445, 455; 544/164, 59, 386; 546/247, 141; 548/530; 540/529

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN structure search- cas online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	Chem. Abs., Volume 127, No. 134690, September 1997, SCHWENDER et al., "Inhibitors of MAdCAM-1-mediated interactions and methods of use therefor".	1
A	US 5,492,896 A (HABICH et al) 20 February 1996, column 1, lines 25-35.	1
A	US 5,516,784 A (BENNETT et al) 14 May 1996, column 1, lines 5-65.	1-26
A,P	US 5,654,301 A (KOHN et al) 05 August 1997, column 1, lines 35-65.	1-26
A,P	US 5,654,451 A (KARI et al) 05 August 1997, column 1, lines 40-65.	1-26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
18 JUNE 1998	30 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DEBORAH LAMBKIN Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/05709

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/05709

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6): C07C 229/00, 241/00, 249/00; C07D 265/30, 279/12, 241/04, 211/30, 217/22, 207/00, 223/10

A. CLASSIFICATION OF SUBJECT MATTER:
US CL : 562/433, 439, 440, 442, 445, 455; 544/164, 59, 386; 546/247, 141; 548/530; 540/529

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. The species are as follows:

Group I, claim(s)1,5,6,8-9,12,17,19-23,25-26, drawn to 7-membered nitrogen containing heterocyclic azacycloheptane compounds, compositions and methods of use.

Group II, claim(s) 1-2,9,14-15,17-20, drawn to 6-membered nitrogen, oxygen and sulfur containing heterocyclic compounds such as morpholines, thiomorpholine, pyridines and pyrimidines, compositions and methods of use.

Group III, claim(s) 1,3,9,11,13,16,17,19-20, drawn to 5-membered nitrogen containing pyrrole compounds, compositions and methods of use.

Group IV, claim(s)1,4,9,17,19-20, drawn to quinoline-type and other benzofused heterocyclic compounds,compositions and methods of use.

Group V, claim(s) 1,7,9-10,17,19-20,22,24, drawn to carboxamide-acid compounds, compositions and methods of use.

The claims are deemed to correspond to the species listed above.

The following claims are generic: 1,9,17,19,20

The various species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

A significant structural element is not shared by all of the alternatives because the common core is a peptide chain which is not novel and furthermore wherein the alternatives are so diverse structurally that one in the art would not expect them to behave in the same or similar manner (MPEP 1850 re Markush Practice).